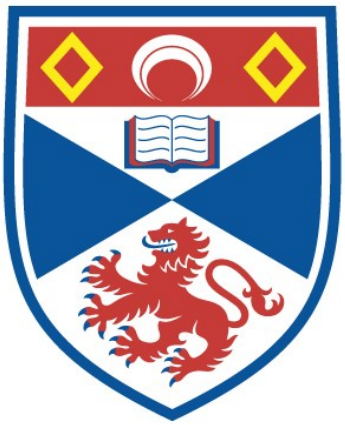
STUDIES IN THE CHEMISTRY OF PYRROLO (2, 1-B) THIAZOLE

Bryan Barnet Molloy

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1963

STUDIES IN THE CHEMISTRY

OF PYRROLO[2,1-b]THIAZOLE.

being a Thesis presented by

BRYAN BARNET MOLLOY.

to the University of St. Andrews in

application for the degree of Ph.D.

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DECLARATION

I hereby declare that the following Thesis is a record of the results of experiments carried out by me, and further that the Thesis is my own composition and has not previously been presented for a higher degree.

The research was carried out in the Department of Chemistry, United College, University of St. Andrews, under the direction of Dr. D.M. Reid.

[redacted]

October 1963

CERTIFICATE

I certify that Bryan Barnet Molloy has spent nine terms at research work under my direction, that he has fulfilled the conditions of Ordinance No.16 (St.Andrews) and is qualified to submit the accompanying Thesis in application for the degree of Ph.D.

Director of Research.

October 1963.

UNIVERSITY CAREER

I first matriculated in the United College of St. Salvator and St. Leonard, University of St. Andrews, in October 1956, and subsequently graduated B.Sc. with First Class Honours in Chemistry in June 1960.

I was admitted as a Research Student in the Department of Chemistry, United College, St. Andrews in September 1960.

I was awarded a Research Studentship by the Carnegie Trust for the Universities of Scotland for the whole of my period as a Research Student.

ACKNOWLEDGEMENTS.

I should like to express my sincere gratitude to Dr. D.H. Reid of the Department of Chemistry, University of St. Andrews for assistance and guidance given to me during the prosecution of the work embodied in the following thesis.

I am grateful to the Carnegie Trust for the Universities of Scotland for the award of a Postgraduate Scholarship.

I should like to thank Drs. A. Melera and W. Bonthrone for Nuclear Magnetic Resonance spectra.

I am also grateful to members of the Technical Staff of the Chemistry Department in St. Andrews who gave of their services, especially Messrs. R. Morris and A. Watson for carrying out the photography required for the presentation of this thesis.

University of St. Andrews.
October, 1963.

EXPLANATORY NOTE

This thesis comprise three parts, Parts A,B and C. Each part is divided into a number of principal sections prefixed by Roman numerals and these sections are divided into sub-sections prefixed by small letters.

Part A deals with the relationship of pyrrolo[2,1-b] thiazole to azulene and indolizine, the chemistry of the latter system being reviewed in detail.

Part B is a discussion of the results achieved in the course of investigations centred on the pyrrolo[2,1-b] thiazole system. Part C is devoted entirely to a description of the experimental details and is the complement to Part B.

Where reference is made to the chemical literature, this is indicated by a number in superscript, keys to which are to be found at the ends of Parts A and C.

CONTENTS

Contents. Part B continued Page

\+ + +

Contents. PART C

SUMMARY

A number of synthetic approaches to the pyrrolo [2,1-b] thiazole system have been investigated. Two useful preparative methods have been developed. The first is based on the cyclisation of the quaternary salts from 2-methyl- or 2-methylene-thiazoles and α-haloketones using sodium acetate in acetic anhydride and leads to a variety of 6-alkyl and 6-aryl pyrrolo [2,1-b] thiazoles. The second method involves the thermal cyclisation of the product from 2-thiazolyl lithium and epichlorohydrin and affords the parent base, although in low yield.

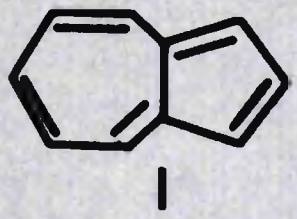
An investigation of the properties of the pyrrolo [2,1-b] thiazole system has been carried out. The ready formation of trinitrobenzene complexes from alkyl pyrrolo [2,1-b] thiazoles together with the evidence afforded by ultra-violet and nuclear magnetic resonance spectroscopy is indicative of the aromatic nature of the system. Pyrrolo [2,1-b] thiazoles readily form salts with picric and perchloric acid. Nuclear magnetic resonance studies have shown that this process, the simplest form of electrophilic attack, involves the 5-position of the nucleus.

A brief examination of the electrophilic substitution reactions of 6-methylpyrrolo [2,1-b] thiazole has shown that substitution takes place extremely readily and that the first substituent group enters at position 5 the second at position 7. An examination of the properties of groups attached to the nucleus has been limited to methyl groups and it has been found in contrast to the analagous indolizine system a methyl group in the 3-position

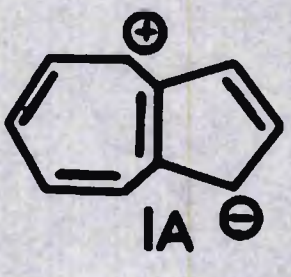
of pyrrolo [2,1-b] thiazole is not sufficiently acidic to allow proton abstraction by n butyl lithium. However methyl groups at the 5- and 7-positions readily suffer abstraction of a hydride ion in analogy to the methyl indolizines.

The results obtained, taken as a whole, indicate a lower degree of polarisation of the ground state of pyrrolo [2,1-b] thiazole than exists in indolizine. Furthermore in the transition state of electrophilic substitution at positions 5 and 7 there appears to be a lesser degree of accomodation of the positive charge on the thiazole ring as compared with similar intermediates in the indolizine series.

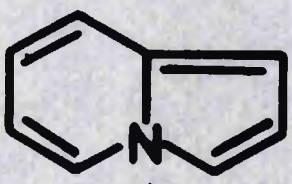
PART A



I



IA



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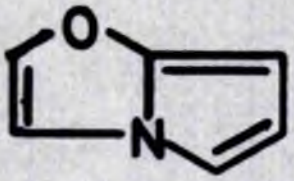

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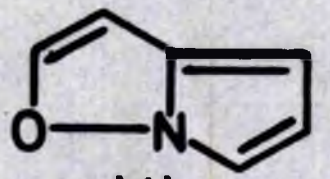

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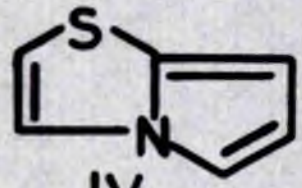

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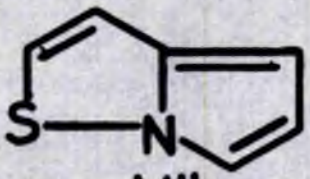

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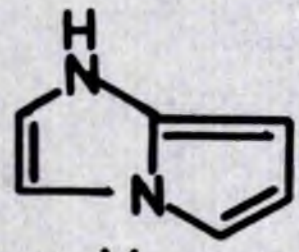

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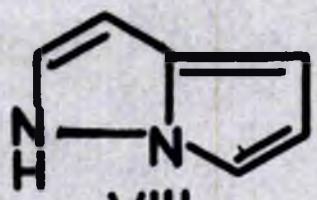


VIII

A1 Azulene and Indolizine

An outstanding feature of the chemistry of azulene(I) and its derivatives is the ease with which these hydrocarbons react with a variety of both electrophilic and nucleophilic reagents, leading to either permanent substitution or the formation of transition type intermediates which may be isolated, utilised in a further reaction, or observed by physiochemical means depending on their stability. This behaviour is determined by a) the ground state polarisation of the molecule and b) its polarisability. The former is recognised in resonance structures such as (IA) and accounts for the observed dipole moment (1·0 D.) as well as the results of theoretical calculations of electron density, predicted to be highest at position 1 and lowest at position 4. The latter, which is of greater importance during reaction, is a measure of the ease with which the π-electron system of the molecule can rearrange to stabilise the ions, or ion like intermediates formed by electrophilic and nucleophilic attack.

One further consequence of the polarisation and ready polarisability of azulene is the considerable electronic interaction between substituents and the π-electron system of the nucleus. This gives rise, for example, to abnormal infra-red spectra of substituted azulenes and uncommon modes of reaction of the substituent groups.

The present research is part of a study of heterocyclic systems possessing a similar polarisation and polarisability. The basic compound of this type is the bridgehead nitrogen heterocycle indolizine(II). Fraser[2] has examined the relationships between indolizine and azulene and these will be dealt with in greater detail

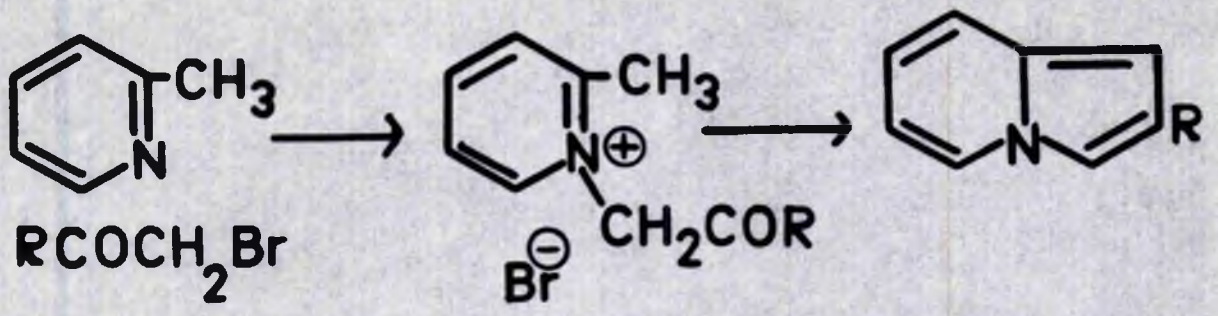
below in a discussion of the properties of indolizine. It was desired to examine the effects of the replacement of either the 5,6 or 7,8 carbon-carbon double-bond of the six membered ring of indolizine by a hetero-atom such as sulphur, oxygen, or nitrogen leading to iso-π-electronic systems pyrrolo[2,1-b]oxazole (III), pyrrolo[2,1-b]thiazole (IV), pyrrolo[2,1-a]imidazole (V), pyrrolo[1,2-b]isoxazole (VI), pyrrolo[1,2-b]isothiazole (VII) and pyrrolo[1,2-b]pyrazole (VIII). The work described in this thesis is concerned with one of these, pyrrolo[2,1-b]thiazole (IV). Since our starting point in this work was the known chemistry of indolizine, we will now consider the synthesis and properties of this compound in greater detail.

AII Indolizine:- Synthetic Methods

Note. Here we are only concerned with preparative methods of possible applicability to the six heterocyclic systems mentioned above, that is to say, only these resulting in the attachment of a five membered ring to the a bond of a pre-existing pyridine ring.

(a) The Scholtz Synthesis.

The first synthesis of indolizines, and until recently [3,4,5] the best method for the preparation of indolizine itself was that studied by Scholtz[6]. He obtained from the reaction of 2-picoline with acetic anhydride at 200°C under pressure a product which was later shown[7] to be 1,3-diacetylindolizine and which on acid hydrolysis afforded indolizine. Replacement of acetic anhydride by propionic anhydride afforded 3-methyl-1-propionylindolizine[8,9,10] and upon subsequent hydrolysis with acid, 3-methylindolizine. This reaction has been extended to some substituted 2-picolines using acetic anhydride[6,11,12] and in each case the products were the fully acetylated derivatives. Boekhelheide[4] applied the reaction using 2,6-lutidine and acetic anhydride in an attempted synthesis of 5-methyl-indolizine and obtained a low yield of 1-acetyl-5-methyl-indolizine. The structural assignment was based on mechanistic grounds[9] and on the fact that hydrolysis of the acetyl derivative to the base with subsequent re-acetylation afforded a different monoacetyl-compound, acetylation of indolizines being known[13] to occur preferentially at the 3 position. The reaction however has not been effected with acid anhydrides other than acetic and propionic[8], and quinaldine will not react with acetic anhydride analagously[14].



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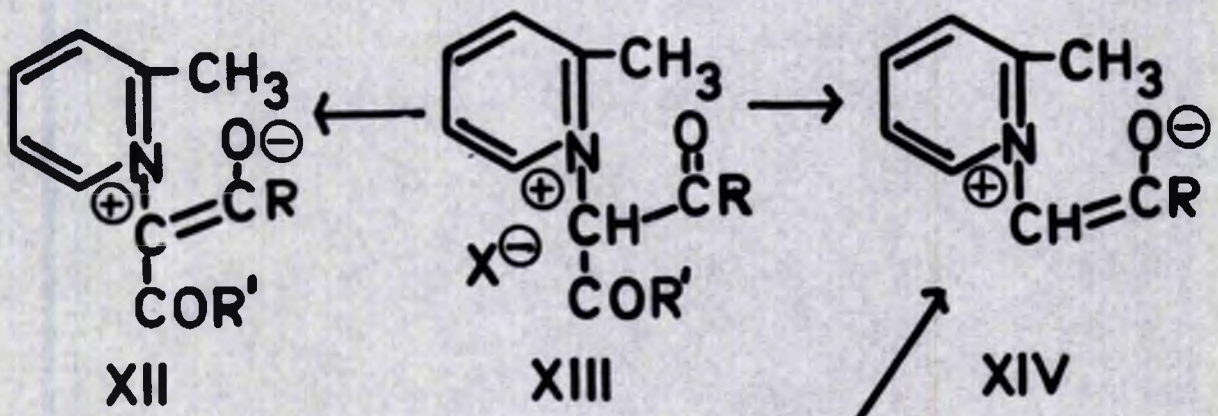
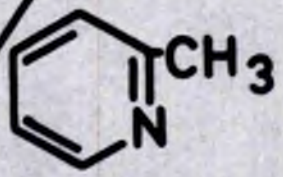
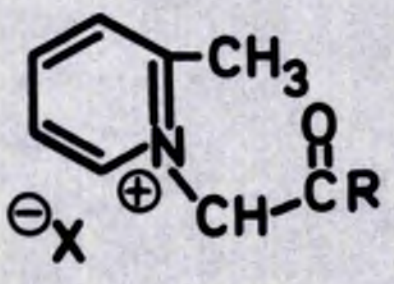


XII XIII XIV





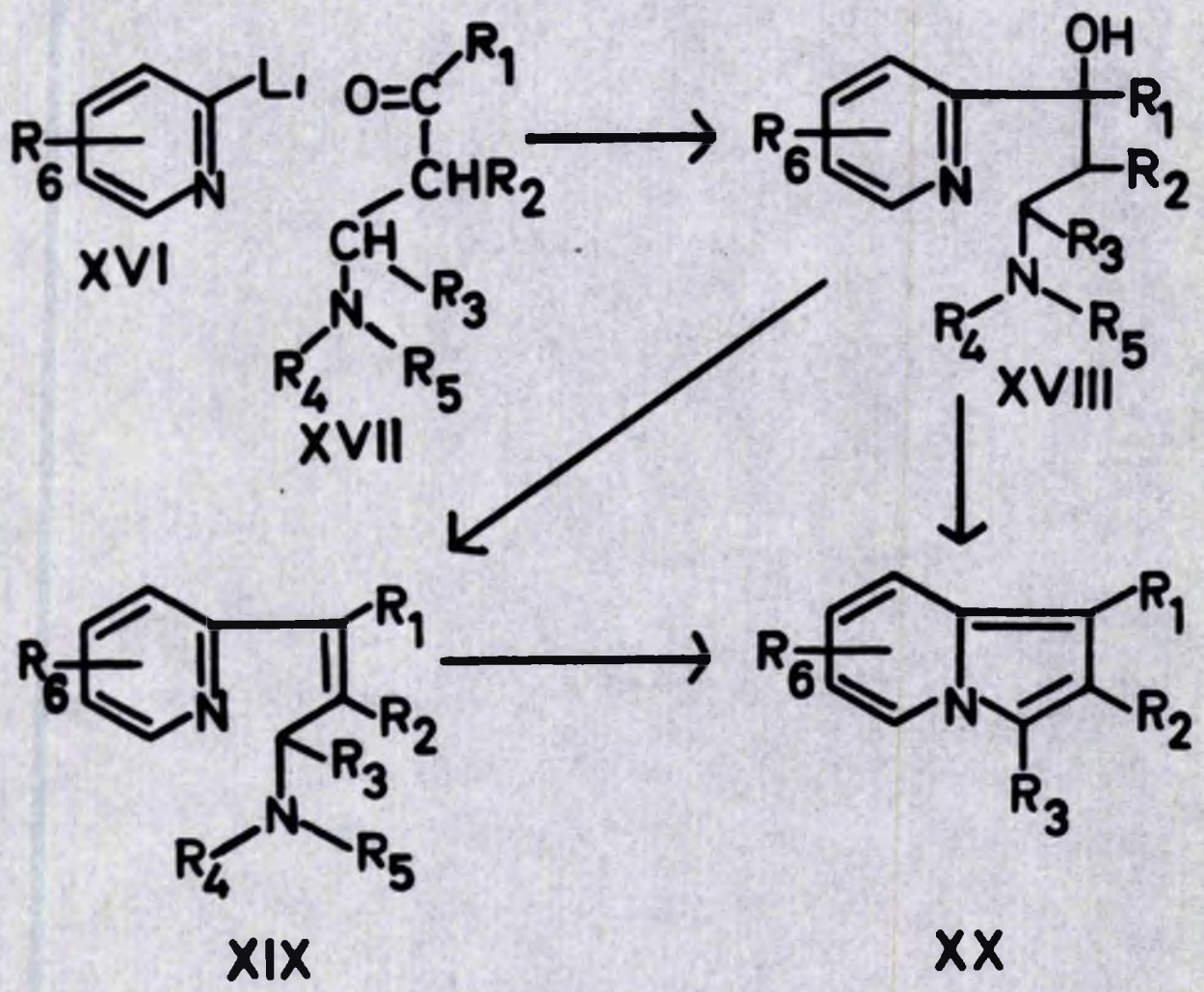
XV

(b) The Chichibabin Synthesis.

By far the most widely utilised method for the formation of indolizines is that devised by Chichibabin[15]. This involves the reaction of an α-halocarbonyl compound with a 2-methyl (methylene) pyridine followed by cyclisation of the resulting quaternary salt with aqueous alkali (IX-XI). Alternatively[16] the reaction of the pyridine with a ketone and iodine or bromine as used by King[17] may be employed for the formation of the quaternary salt. An attempt[15] to apply the reaction to the preparation of indolizine itself by the reaction of 2-picoline with α-bromoacetaldehyde, its diethyl acetal, or dimer afforded the desired product in only 1% yield, but in the preparation of 2-alkyl and especially 2-aryl indolizines the yields are usually good.

Optimum yields are obtained using bromo- rather than chloro-carbonyl compounds[13], especially those in which neither the halogen atom[14] nor the carbonyl[18] group is sterically hindered. The use of 6-substituted-2-picolines leads to poor yields due to steric effects.[15,19,20] The nature of base used for cyclisation affects the yields also, weak bases such as carbonates and bicarbonates being more effective than hydroxides.

In an attempt to prepare indolizines substituted with suitable functional groups for orientation studies Borrows, Holland and Kenyon[16] attempted the reaction using 2-picoline with α-chloroacetylacetone, α-bromobenzoylacetone, ethyl α-chloroacetoacetate and ethyl α-bromobenzoylacetate. Difficulties were experienced in the preparation of the quaternary salts and upon attempted cyclisation loss of the acyl, or ester function occurred. The failure of these

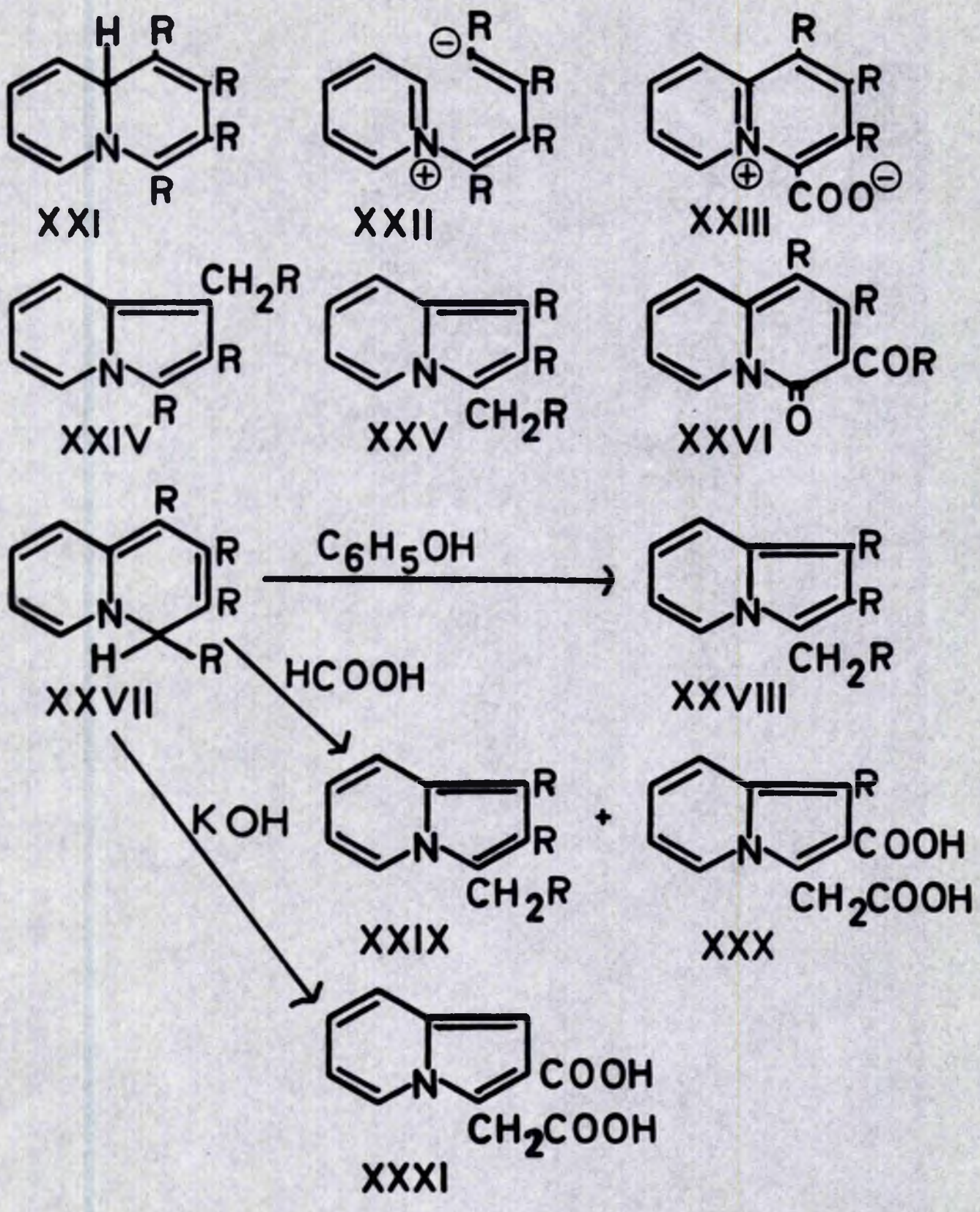

Li
O=C
R1
CHR2
CH
R3
N
R4
R5
R6
N
XVI
XVII
OH
R1
R2
R3
N
R4
R5
XVIII
R1
R2
R3
N
R4
R5
R6
N
XIX
R1
R2
R3
R6
N
XX

experiments is explained by the nature of the intermediates formed during cyclisation. Krohnke[21,22,23] has shown that the nature of the enol-betaine formed by the treatment of quaternary salts such as (XIII) with a base depends on the structure of the salt and on the strength of the base used. The use of a weak base leads to enol-betaines of type (XII), whereas a stronger base leads to acyl cleavage and an enol-betaine of type (XIV). The postulation of enol-betaines of type (XIV) as intermediates in the Chichibabin synthesis serves furthermore to explain the observed production of 2-picoline hydrohalides during some quaternisations, the picoline itself being a sufficiently strong base to abstract a proton from the quaternary salt (XV) with the formation of (XIV). However despite the lability of acyl groups in salts of type (XIII) the reaction[26] of 2-picoline with 3-chloroisonitrosoacetophenone afforded after cyclisation 3-nitroso-2-phenylindolizine but a similar reaction using 3-bromo-3-nitroacetophenone failed at the quaternisation step..

The synthesis can be applied to 1-halo-2,3-dicarbonyl compounds. Iododiacetyl[24] and ethyl bromopyrurate lead to 2-acetyl-and 2-carboxyindolizine, respectively, the latter affording indolizine itself upon decarboxylation. Attempts[16] to apply the synthesis to the benzo[a]indolizine series by the reaction of quinaldine with chloroacetone and phenacyl bromide failed at the quaternisation stages, quinaldine hydrohalides only being produced.

(c) <u>The Barret Synthesis</u>.

The method devised by Barret and co-workers[27,28,29,12] makes use of Mannich bases to provide the three carbon unit for attachment to a pyridine ring. Reaction of a

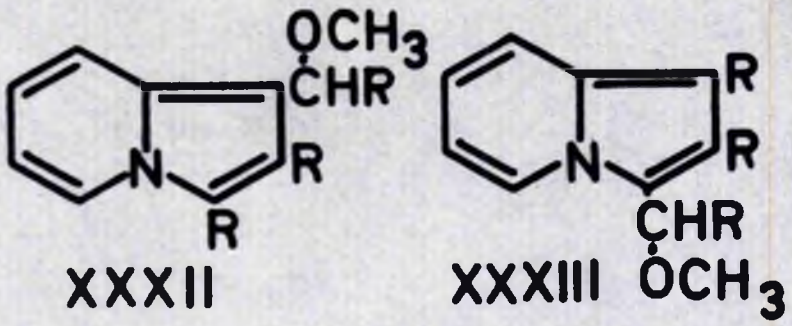

XXI
XXII
XXIII
XXIV
XXV
XXVI
XXVII
XXVIII
XXIX
XXX
XXXI
C6H5OH
HCOOH
KOH
[R=COOCH3]

2-pyridyl lithium(XVI) with the Mannich base (XVII) affords the alcohol (XVIII) which is dehydrated by sulphuric acid to the olefine (XIX). Refluxing either (XVIII) or (XIX) with acetic anhydride for several hours produces the indolizine (XX). The yields are variable and are generally greater when R_1 is alkyl rather than aryl. In cases when R_3 in (XVIII) or (XIX) is hydrogen acetylation of the resulting indolizine at the vacant 3-position occurs so that R_3=$COCH_3$ in (XX). An examination of the mechanism of the cyclisation and the many by-products has shown that the reactions are exceedingly complex, but it is known that the cyclisation of (XVIII) to (XX) does not proceed via the olefine (XIX) but through an acetoxy compound.

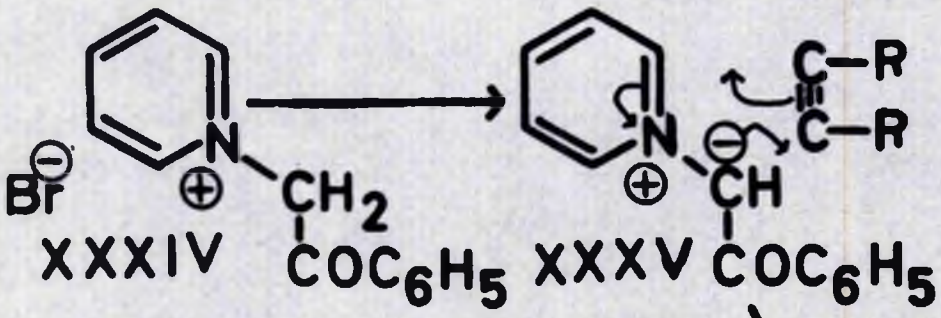
(d) Synthesis utilising Dimethyl Acetylenedicarboxylate.

Diels and his collaborators[30,31,32] in their work on the reaction of pyridine with dimethyl acetylenedicarboxylate in ether isolated three quinolizine derivatives, a yellow "stable" adduct, a red "labile" adduct and the so called "Kashimoto" compound which were formulated as (XXI), (XXII) and (XXIII) respectively. The "labile" adduct was readily converted into the "stable" adduct and this compound afforded trimethyl indolizine-1,2,3-tricarboxylate on oxidation. Treatment of the "stable" adduct with phenol or formic acid[33,34] afforded a tricarboxylic ester formulated initially as (XXIV) but later as (XXV).

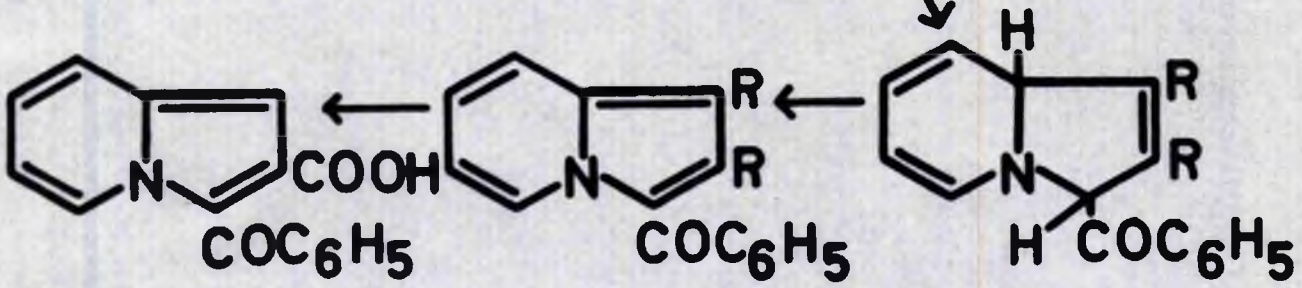
Subsequent examination[35] of this work resulted in the isolation of trimethyl indolizine-1,2,3-tricarboxylate but it is considered that the production of this compound is dependent on the presence of traces of peroxides and



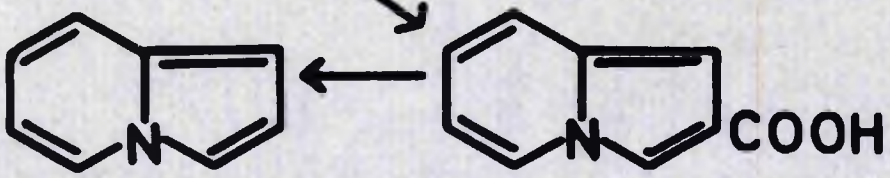
XXXII XXXIII



XXXIV XXXV



XXXVIII XXXVII XXXVI



XL XXXIX

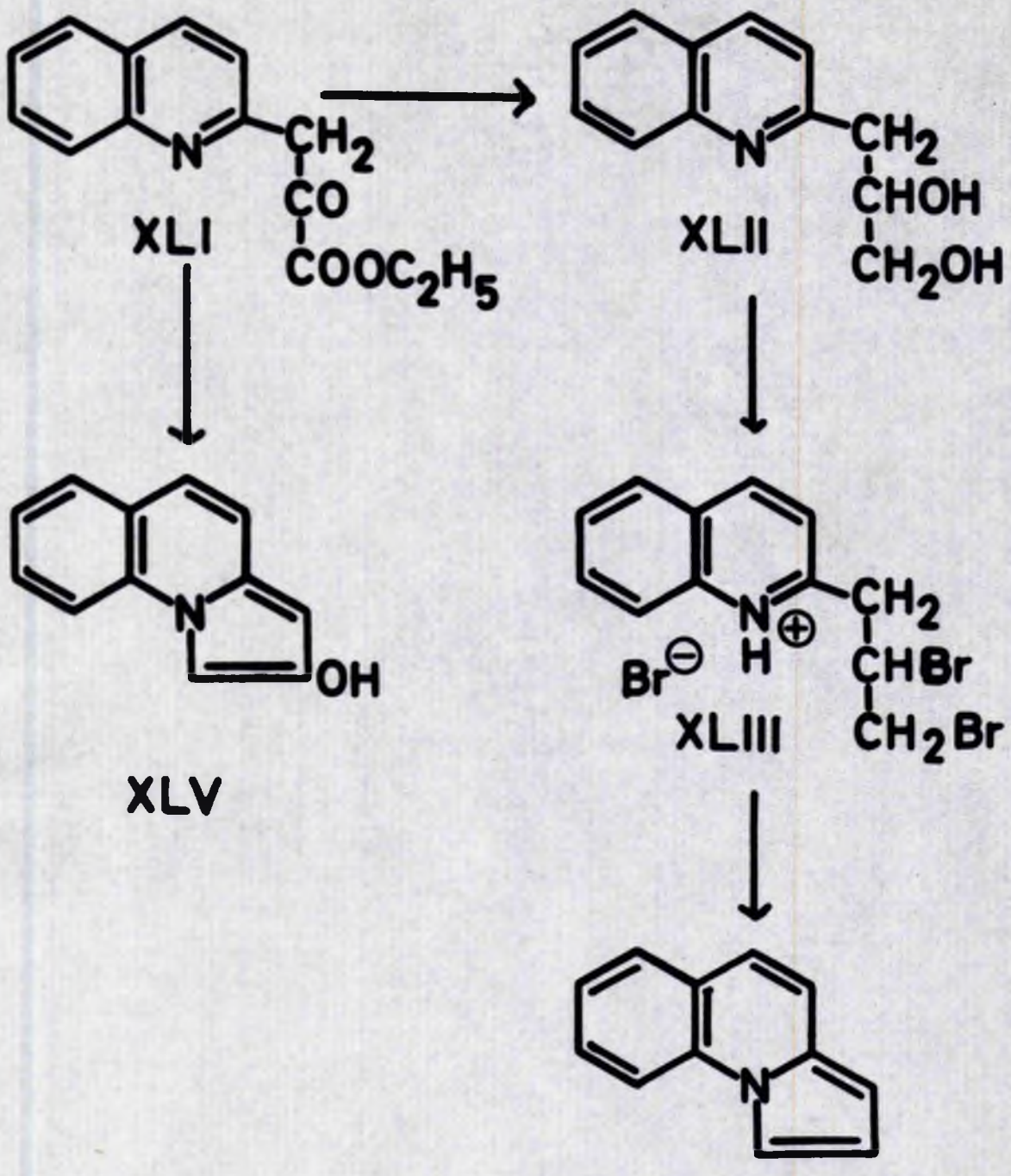
[R=COOCH$_3$]

ethanol. The structure of the "Kashimoto" compound has been shown[36] to be (XXVI). Acheson and co-workers[37] were unable to isolate the labile adduct and showed that the stable adduct in fact possessed structure (XXVII) but confirmed its oxidation to trimethyl indolizine-1,2,3-tricarboxylate. An examination[38] of the reactions of (XXVII) with phenol, formic acid and potassium hydroxide showed that the products were derivatives of indolizine-3-acetic acid as shown in the reaction scheme (XXVII) - (XXXI).

Diels and Meyer[33] found that the reaction in methanol in which the pyridine is added to methanolic dimethyl acetylenedicarboxylate afforded trimethyl indolizine-1,2,3-tricarboxylate when the reaction proceeded without cooling but at 0°C, the product also contained a trimethyl methoxymethylindolizinetricarboxylate formulated as (XXXII). The latter was converted into the former by treatment with bromine in methanol or acetic acid. Later attempts to repeat[25,39] this work afforded only the compound formulated as (XXXII), and Johnson and co-workers established[39] that it actually possesses structure (XXXIII). A mechanism has been proposed[40] to account for the formation of the two products isolated by Diels.

The material surveyed above represents only a fraction of the wealth of experimental evidence available[41] on the pyridine-acetylenic ester addition reaction but should be sufficient to indicate the potential of this method of synthesis.

Boekelheide[42] has prepared indolizines by reaction of the zwitterions derived from N-phenacylpyridinium salts by treatment with alkali, with dimethyl acetylenedicar-

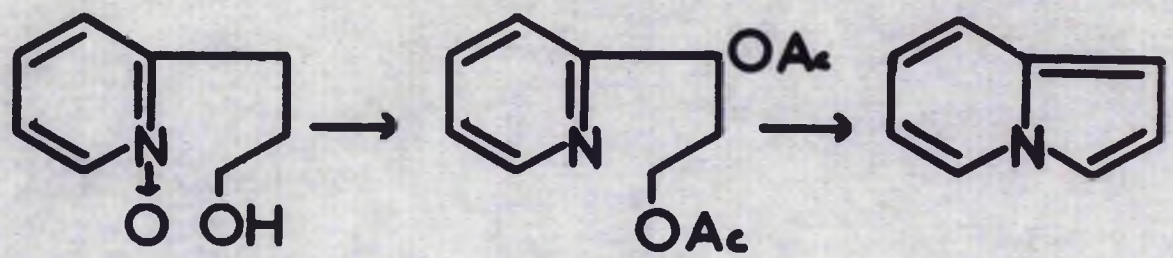

CH2
CO
COOC2H5
XLI
CH2
CHOH
CH2OH
XLII
OH
XLV
N
H
Br
CH2
CHBr
CH2Br
XLIII
XLIV

boxylate in the presence of a palladium-on-charcoal catalyst, e.g. (XXXIV) - (XXXVII). Reaction proceeds by a Michael type addition of the switterion to the ester followed by cyclisation at position 2 of the pyridine nucleus and dehydrogenation and affords dimethyl 3-benzoyl-lindolizine-1,2-dicarboxylate (XXXVII). The substituent groups are readily removed by alkaline hydrolysis and acidification, giving the keto acid (XXXVIII). Acid hydrolysis of the latter affords the acid (XXXIX) which is decarboxylated to the indolizine (XL).

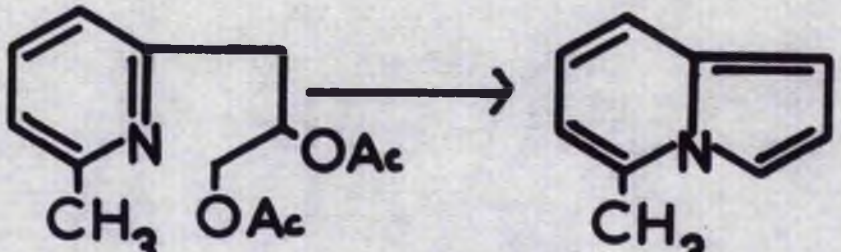
(c) Syntheses utilising substituted 2-n propylpyridines

These syntheses, which have been developed by Boekelheide and co-workers, provide routes mainly to indolizines unsubstituted in the five-membered ring, and one complementary to the Chichibabin and Barret methods. Sodium borohydride reduction of the pyruvic ester (XLI) from quinaldine and diethyl oxalate afforded the diol (XLII) which, by successive treatment with hydrobromic acid and alkali[43], was cyclised to the indolizine (XLIV) via the dibromo compound(XLIII). The yield over steps (XLII) - (XLIV) is 85%. Perhaps the most surprising feature of this reaction is the facile reduction of the keto ester by borohydride, the use of lithium aluminium hydride leading to the product(XLV).

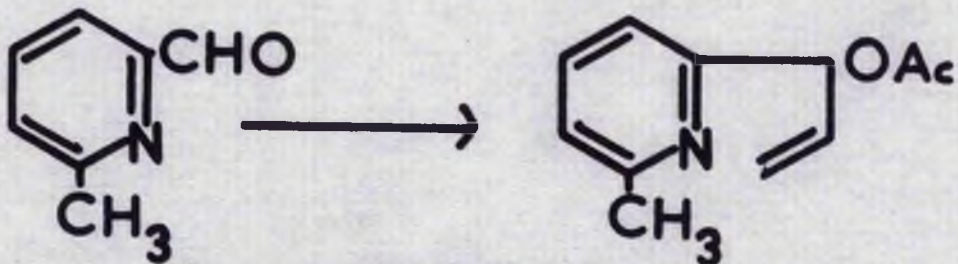
Indolizine (XLVIII) itself was synthesised[44] by the pyrolysis of the diacetate(XLVII), prepared by the action of acetic anhydride on the N-oxide of 3-(2-pyridyl)-1-propanol(XLVI). Attempts[5] to apply this method to the preparation of 5-methylindolizine (L) by the pyrolysis of the isomeric diacetate (LI), prepared in a similar manner



XLVI XLVII XLVIII



IL L



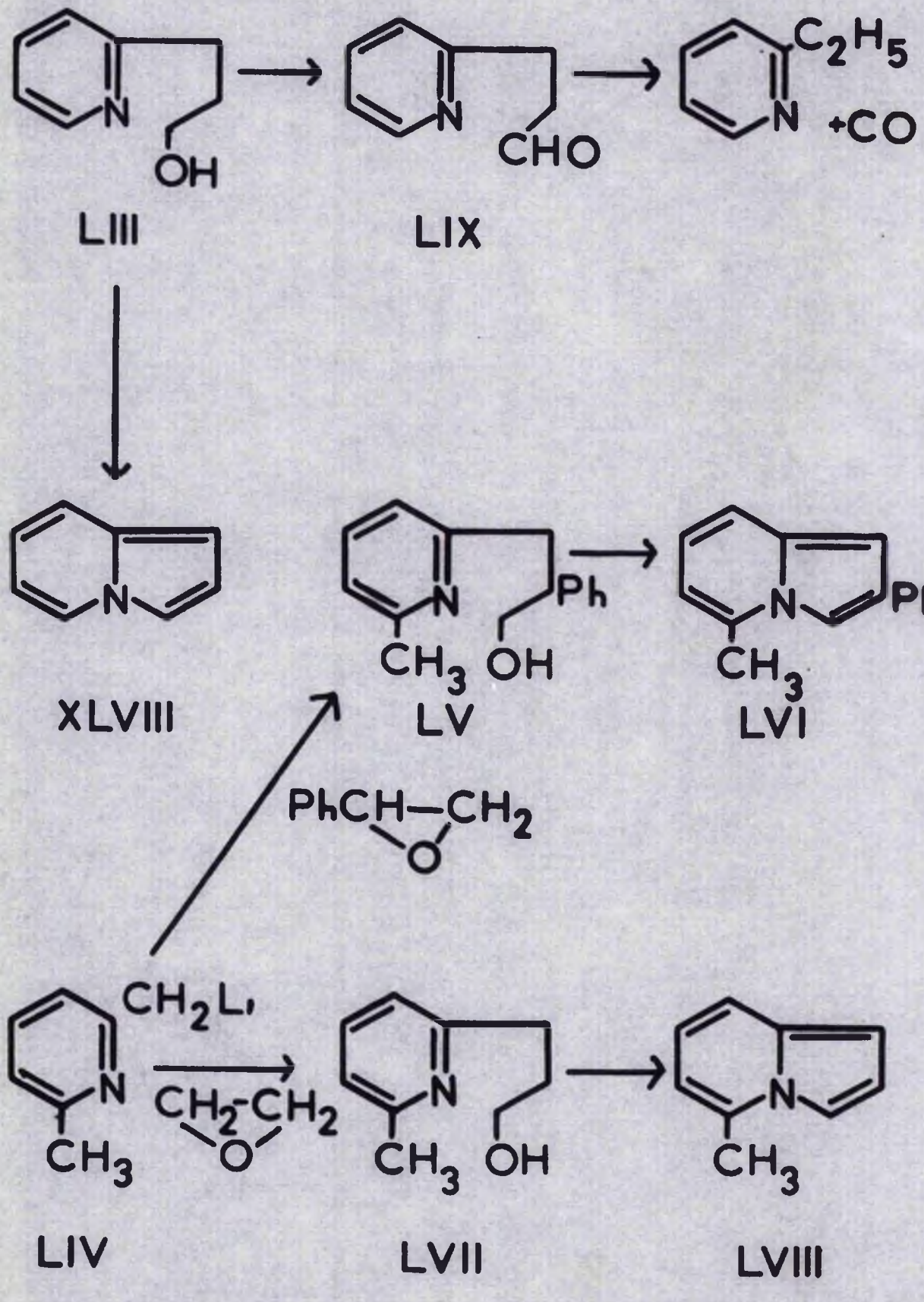
LI LII

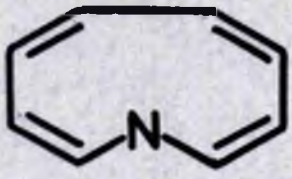
1) $CH_2=CHMgBr$

2) Ac_2O

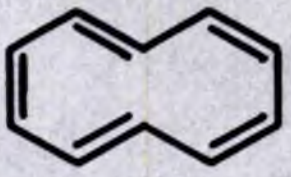
to (LII), afforded the desired product in poor yield but the synthesis was realised[5] by the pyrolysis of the ester (LII) prepared as shown.

A superior method[5] for the preparation of indolizine consists of the cyclodehydration-dehydrogeration of 3-(2-pyridyl)-1-propanol (LIII) in the presence of palladium-on-charcoal. The yield is about 50%. The reaction is applicable also to the preparation of 2-phenyl-5-methylindolizine (LVI)[5] and 5-methylindolizine (LVIII)[4]. A more detailed examination[4] of the preparation of indolizine itself has shown that carbon monoxide and 2-ethylpyridine are by-products, suggesting the participation of 3-(2-pyridyl)-propionaldelyde (LIX).

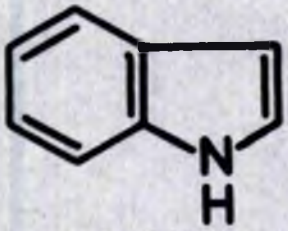

OH
N
CHO
C_2H_5
+CO
LIII
LIX
XLVIII
Ph
CH_3
OH
LV
LVI
$PhCH-CH_2$
O
CH_2Li
CH_2-CH_2
LIV
LVII
LVIII



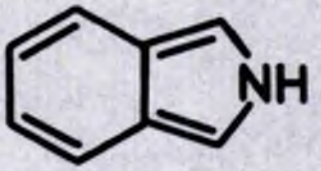
LX



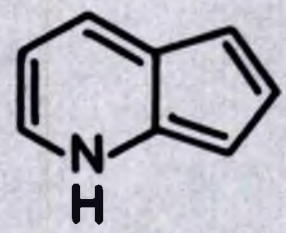
LXI



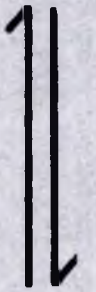
LXII

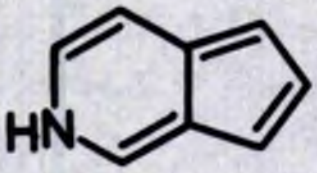


LXIII

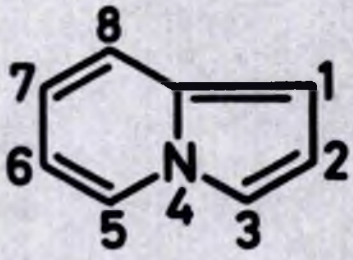


LXIV

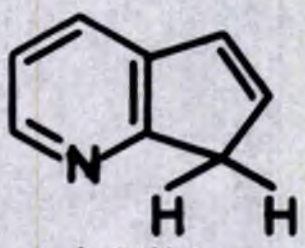




LXV



LXVI



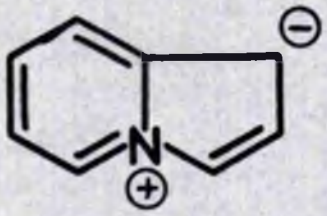
LXIVa

AIII Indolizine:- Properties

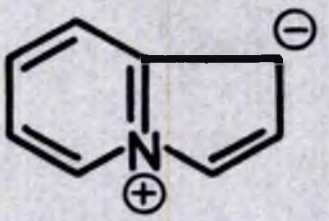
a) Theoretical Considerations

Indolizine may be regarded as 1-azacyclonona-2,4,6,8-tetraene (LX) with a formal transannular valency bridge, as in the case of the isoelectronic cyclodecapentaene (LXI) which can be regarded as the monocyclic precursor of napthalene and azulene the heterocycle would not be expected to be stable due to the mutual inside interference of hydrogen atoms[45,46,47] giving rise to such strains in a planar system as to exceed the resonance energy of the planar state. Just as transannular bond formation in (LXI) gives rise to azulene and napthalene, compounds with widely differing properties, so this process applied to (LX) affords a range of widely differing heterocyclic compounds, indole (LXII), isoindole (LXIII), the azulene analogues (LXIV)and (LXV) and indolizine (LXVI).

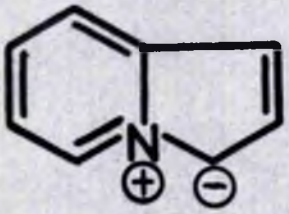
The reactivity of indole is that of a typical pyrrole derivative and might be described as "enhanced benzenoid reactivity". Little is known, however of the chemistry of (LXIII), (LXIV) and (LXV) save that (LXIV) exists[48] predominantly in the tautomeric pyrindene form (LXIVa). Recognition of the essential aromatic character of indolizine is of recent origin.[49,40,51,52] The resonance energy has been calculated[52] to be 52 k.cals./mole. though a later paper[53] suggests a figure 10 k.cals. higher, placing it alongside azulene(49)[54] and indole (47[55] or 54[56]). A consideration[49] of the dipolar forms contributing to the resonance hybrid shows that two forms place the negative charge at the 1-position, two place it at the 3-position (LXVII)-(LXX), but the forms having the



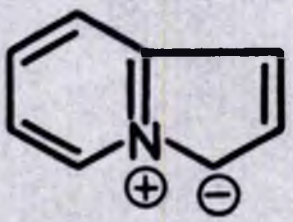
LXVII



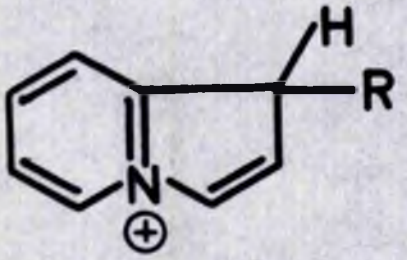
LXVIII



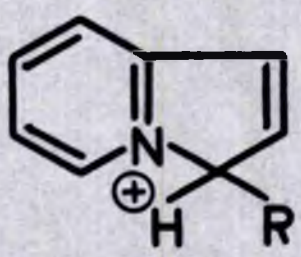
LXIX



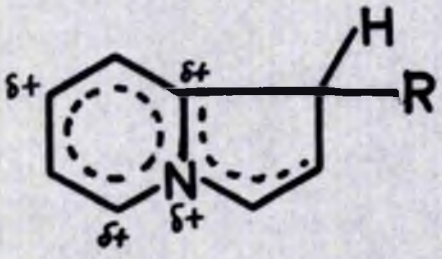
LXX



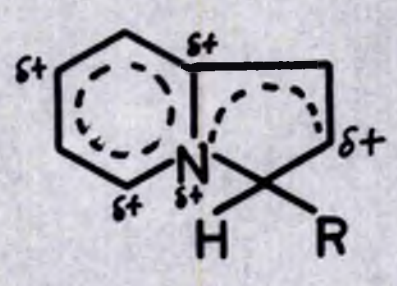
LXXI



LXXII



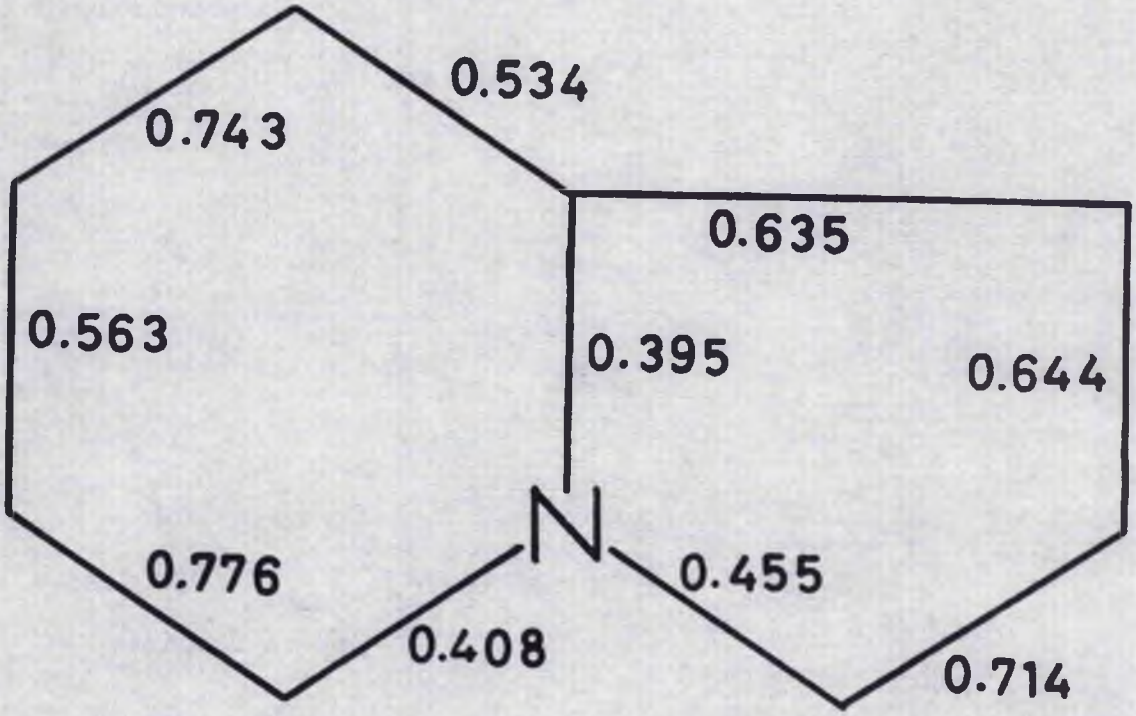
LXXIV



LXXIII

negative charge at the 2,5,6,7,8 and 8a positions each occur only once. This approach together with the observation[4] that in the transition states for electrophilic substitution an intact pyridinium ring is present only if attack takes place at positions 1(LXXI) or 3 (LXXII) suggests that these would be the sites of electrophilic attack. However of the contributing forms of (LXXI) three have the positive charge on carbon (LXXIV) as opposed to four (LXXIII) in the case of (LXXII) suggesting electrophilic attack at position 3[4].

Longust-Higgins and Coulson[51] have calculated the mobile bond orders and π-electron densities for indolizine. These are shown in (LXXV) and Table I, respectively. As in the case of azulene, the bridging bond has the lowest order, indicating a high degree of peripheral π-electron delocalisation. According to the table of -electron densities electrophilic substitution would take place most easily at position 3, then at position 1 followed by position 5 or 2. Nucleophilic substitution was not expected to occur readily since no carbon atom bears an unusually low electron density. In table I column (2) are shown the results of a calculation[57] of the "frontier electron" densities for electrophilic substitution. This method is based on a concept that the pair of π-electrons in the highest energy molecular orbital of the ground state are decisive in electrophilic attack. These are denoted the "frontier electrons" and their density at each peripheral atom calculated by the L.C.A.O. method. There is good qualitative agreement between the two sets of results as regards positions I



LXXV

and 3, but the latter indicate a greatly reduced reactivity for the 5 position.

Table I

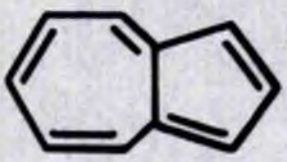
Position	π-Electron density.[51]	Frontier electron density.[57]	Atom Localisation energies[4].		
			Electrophilic attack.	Radical attack.	Nucleophilic attack.
1	1.127	0.454	1.815	2.410	2.987
2	1.037	0.031	2.287	2.546	2.805
3	1.182	0.527	1.854	2.448	3.043
4	1.589	0.033	---	---	---
5	1.045	0.289	2.155	2.280	2.405
6	0.980	0.141	2.293	2.470	2.647
7	1.003	0.191	2.255	2.432	2.609
8	0.964	0.218	2.152	2.274	2.395
8a	---	0.086	---	---	---

Table II

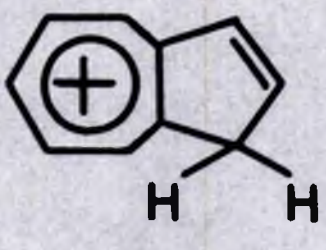
Bond Localisation Energies for Indolizine

Bond	Localisation energy	Bond	Localisation energy
1-2	3.479	7-8	3.224
2-3	3.482	1-8	4.329
3-6	3.181	3-5	4.255
6-7	3.773	5-8	3.694

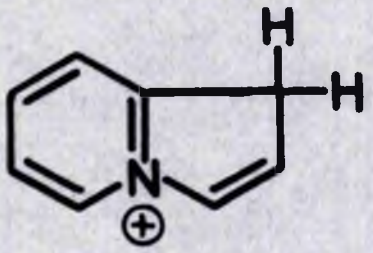
Boekelheide[4] has calculated the atom localisation energies for electrophilic, radical and nucleophilic attack of indolizine (table I) as well as the bond



LXXVI

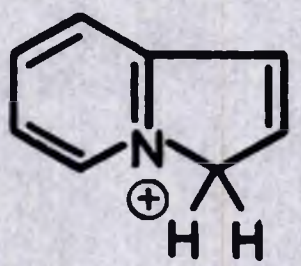


LXXVII

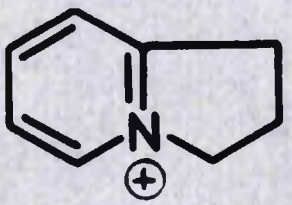


a

LXXVIII



b



LXXIX

localisation energies (table II). These results predict ready electrophilic substitution at positions 1 and 3 in that order and nucleophilic and radical attack in the six membered ring at either position 5 or 8. Addition reactions involving attack at two adjacent centres, such as ozonolysis, would be expected to occur at the 5-6 bond and those involving two non-adjacent centres, such as Diels-Alder addition, at the 5-8 position.

b) Electrophilic attack.

The most notable feature of the substitution chemistry of indolizines is the lack of evidence concerning the reactions and product orientations of the parent base. To date the only compounds which have been subjected to systematic orientation studies are the 2-methyl- and 2-phenyl-derivatives. Work on the latter is complicated by the isolation of products involving reaction in the benzene ring, probably a result of attack on a protonated molecule, and such products will in the main be ignored in the following discussion. In almost all of the orientation work described below use has been made of the hydrogen peroxide oxidation of substituted indolizines. The isolation in all cases of 2-picolinic acid-N-oxide eliminates the possibility of substitution having occurred in the six membered ring.

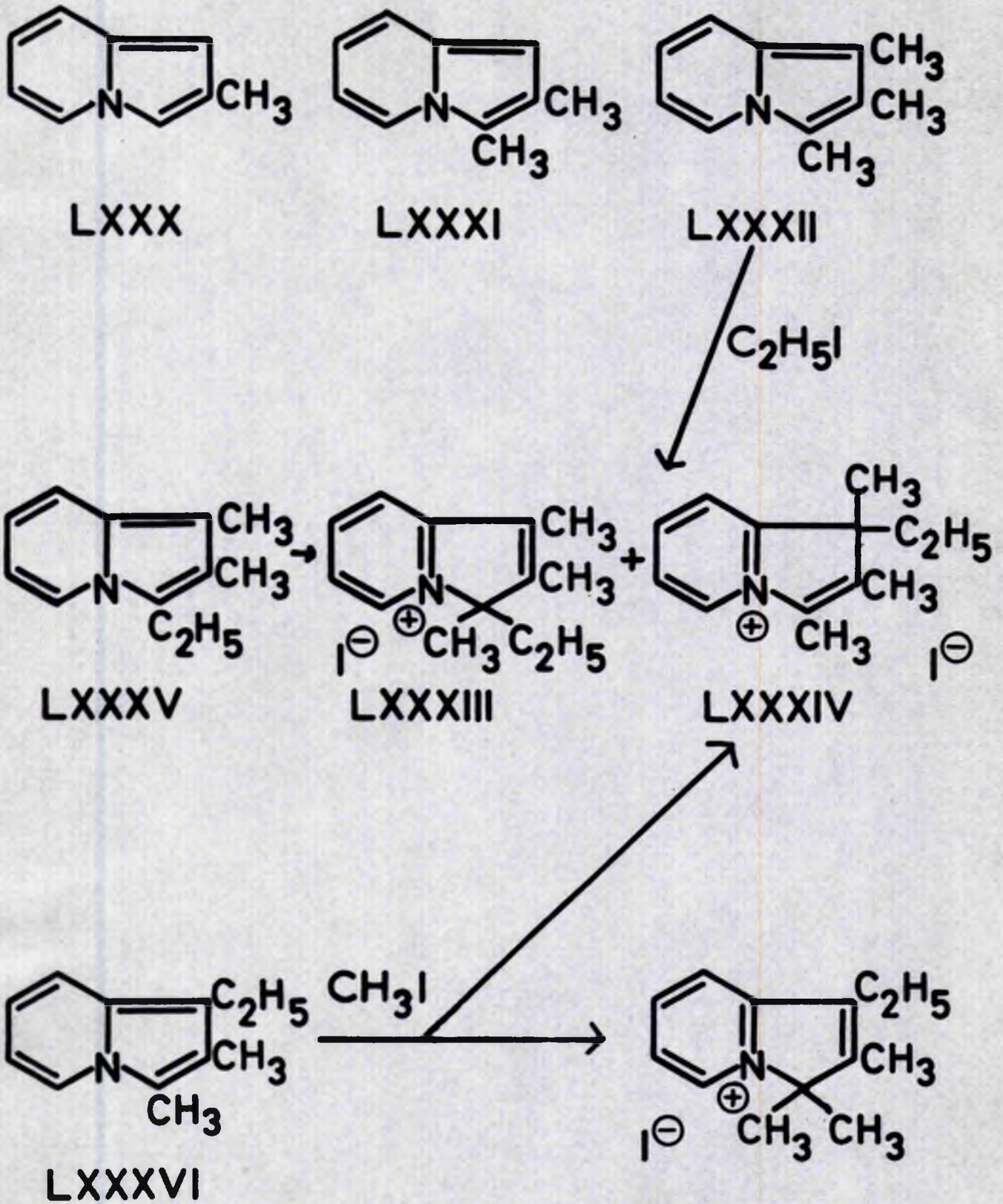
(1) Protonation.

The protonation of a molecule can be regarded as the simplest form of electrophilic attack. The reversible solubility of azulene (LXXVI) in acids is one of the most striking features[58] of the chemistry of this

hydrocarbon. Recently stable crystalline salts of azulenes with strong acids have been isolated[59,60] and theoretical predictions[61,62] that protonation occurs at C-1(3) (LXXVII) have been confirmed by nuclear magnetic resonance studies[63].

The base strengths of indolizine and some alkyl derivatives have been measured[64] in 60% ethanol affording values ranging from pK_B 11.37 for indolizine to pK_B 8.57 for 1,2-dimethylindolizine. Introduction of methyl groups into the nucleus causes a fairly large cumulative decrease of pK_B except when the 3 position is involved, in which case a small decrease or increase is observed, suggesting that this site is involved in protonation. In spite of their low basicity indolizines form stable crystalline salts with strong acids, perchloric acid being considered[2] best for this purpose. The theoretical considerations summarised above suggest protonation on nitrogen, C-1 or C-3. Rossiter and Saxton[65] consider that the indolizinium cation results from protonation on C-1 (LXXVIIIa) or C-3 (LXXVIIIb). This view is supported by the observation[66] that catalytic hydrogenation of indolizine dissolved in hydrobromic acid occurs in the five membered ring, affording the salt (LXXIX). The double bond extracyclic to the pyridinium ring in (LXXVIIIa) or (LXXVIIIb), like that in the five-membered ring of the azulenium ion (LXXVII)[63], would possess considerable olefinic character.

We[67] have examined the proton magnetic resonance spectra of a number of indolizines dissolved in trifluoroacetic acid and have been able to show that in all the compounds studied protonation takes place


LXXX
LXXXI
LXXXII
C2H5I
LXXXV
LXXXIII
LXXXIV
CH3I
LXXXVI

entirely at C-3 except in the cases of 3-methyl-2-phenylindolizine (10% at C-1) and 2,3-dimethylindolizine (50% at C-1) presumably due to steric reasons. Furthermore no proton exchange takes place between cation and solvent even in the case of the most weakly basic 2-phenylindolizine.

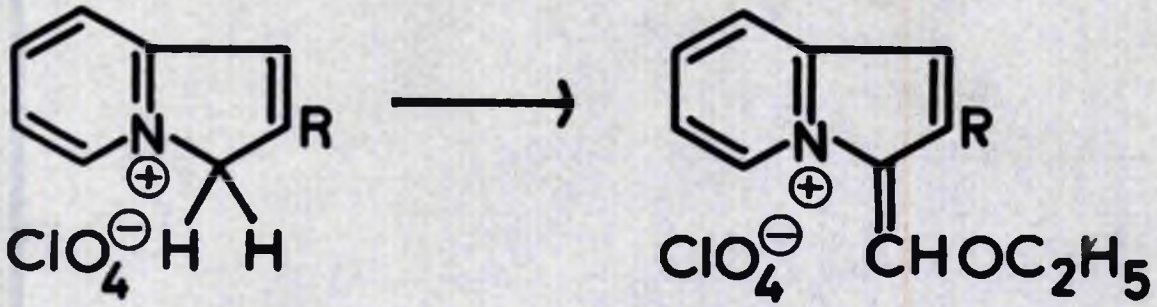
(2) Alkylation.

Indolizines are readily alkylated by treatment with alkyl halides. Reaction of 2-methylindolizine (LXXX) with methyl iodide afforded 2,3-dimethylindolizine (LXXXI) and thence, 1,2,3-trimethylindolizine (LXXXII).[65] Treatment of the latter with ethyl iodide[19] afforded a mixture of the salts (LXXXIII) (mainly) and (LXXXIV), which were also produced by methylation of the ethylindolizines (LXXXV) and (LXXXVI). The structures of the products are thereby orientated.

(3) Acylation.

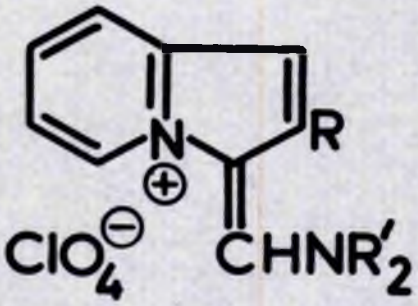
Indolizines are extremely vulnerable to mild acylating agents. Treatment of the bases with acid anhydrides in the presence of the sodium salt of the corresponding acid readily yields the monoacetyl- and monobenzoyl-derivatives of 2-methyl- and 2-phenylindolizine.[7,16] Under more vigorous conditions diacetylation may be achieved. The monobenzoylindolizines may also be prepared[8,16,68] by reaction with benzoyl chloride without a catalyst. This behaviour is similar to that of azulene[87]. In contrast however acetyl chloride and bromide require the presence of a catalyst for reaction with 2-phenylindolizine[14].

Removal of the acyl group is readily effected by

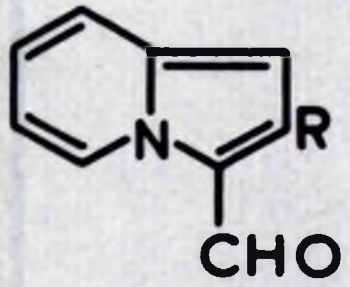


LXXXVII

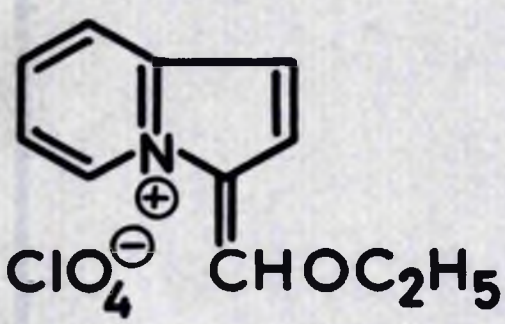
LXXXVIII



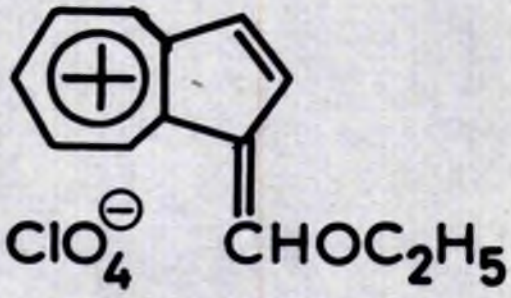
LXXXIX



XC



XCI



XCII

acid[7,16,28,29], another analogy to azulene chemistry[58], but this process is hindered by the presence of electron-attracting groups in the nucleus.[16,26,69,70]

The orientation of the monoacetyl and monobenzoyl derivatives of 2-methyl-, and 2-phenylindolizine has been established[13,68] by the reduction of the acyl group to alkyl using various methods. Comparison of the products with material prepared by the Chichibabin synthesis has shown them to be 3-substituted.

Formylation of indolizines is readily effected by means of the Vilsmeier reaction using phosphorus oxychloride and N-methylformanilide or dimethyl formamide.[65,68,71] The products are mono- or di-formylated according to the control of quantities and conditions exercised. Fraser[2] has applied a more satisfactory method taken from azulene chemistry[72]. Reaction of the indolizine as the perchlorate (LXXXVII) in alcoholic solution with a large excess of triethyl orthoformate affords an ethoxymethyleneindolizinium salt (LXXXVIII) which on reaction with a secondary amine affords the amino-methyleneindolizinium salt (LXXXIX). This undergoes ready hydrolysis to the aldehyde (XC). It is interesting to note that the cation of (LXXXIX) is identical to the intermediate of the Vilsmeier reaction. This method is not applicable to indolizine itself nor, as has already been shown[72], to azulene, the salts (XCI) and (XCII) are not sufficiently stable to permit their isolation. The presence of electron releasing substituents however stabilises such salts in both series, allowing the reaction to be applied.

The orientation of the monoformyl-2-methylindolizine

has been determined[65] as the 3-substituted compound since reduction by the Wolff-Kishner method or by the use of lithium aluminium hydride afforded the known 2,3-dimethylindolizine.

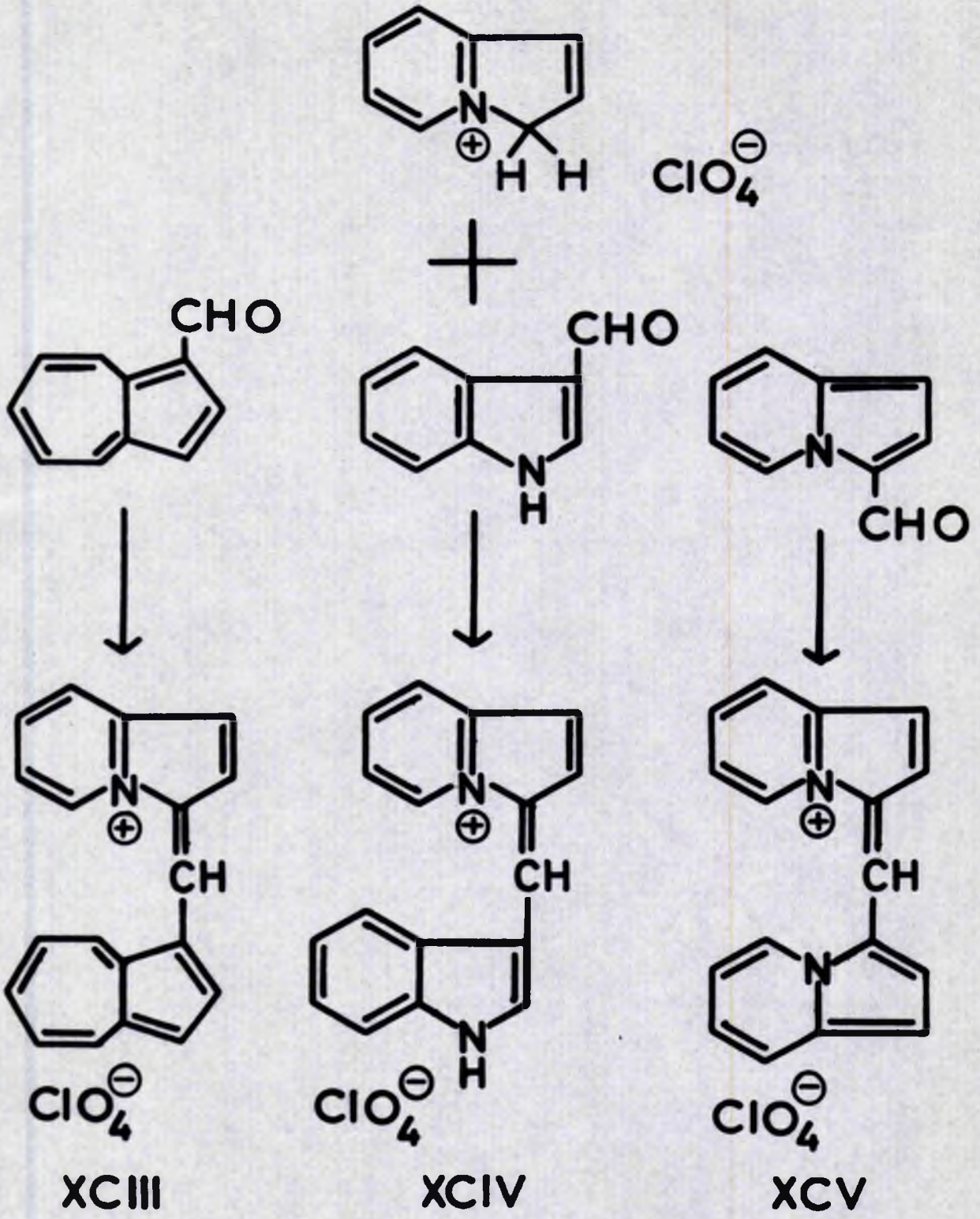
(4) Nitration.

Borrows, Holland and Kenyon[69] found that nitration of 2-substituted indolizines proceeded fairly smoothly using nitric acid at fairly high temperatures for short reaction times or alternatively in admixture with sulphuric acid at low temperatures. The use of nitric acid for prolonged periods at moderate temperatures led to considerable oxidative degradation, due presumably to an increase in the relative rate of oxidation compared with nitration on decreasing the temperature. A similar result was obtained in the case of indolizine itself.[70]

Nitration of 2-methylindolizine afforded two mononitro compounds[69] in the ratio of about 40:1 along with a 1,3-dinitro compound. The main product is surprisingly the 1-nitro isomer since on acetylation it affords the same nitro-acetyl compound as is formed by the nitration of 3-acetylindolizine. Nitration of 1,3-diacetylindolizine[70,73] and its 2-methyl and 2-phenyl analogues[69] causes a facile replacement of acetyl groups by nitro, the products being 3-acetyl-1-nitroindolizines and under more vigorous conditions 1,3-dinitro compounds.

(5) Nitrosation.

Indolizines are readily nitrosated[26] by the action of sodium nitrite on solutions of the bases in aqueous acid. The products are exclusively monosubstituted. The mononitroso 2-methyl- and 2-phenyl-indolizines are the



XCIII XCIV XCV

3-nitroso compounds as shown by the oxidation of the former with hydrogen peroxide in acetic acid to the known 2-methyl-3-nitroindolizine and the direct synthesis of the latter by the Chichibabin method from ω-isonitrosophenacyl chloride and 2-picoline.

(6) Condensation with aldehydes.

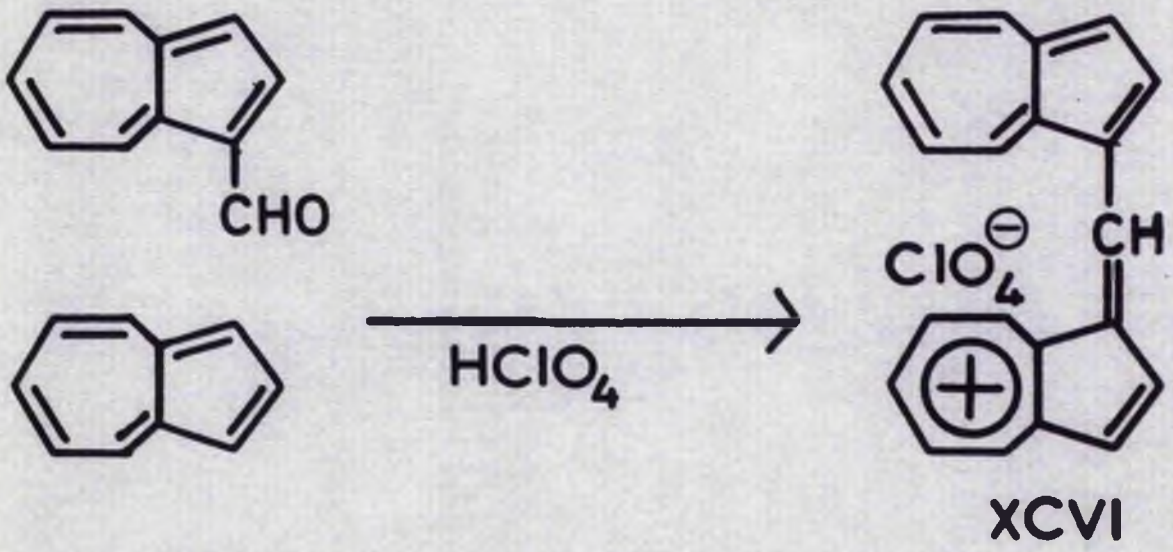
In recent years one of the largest developments in the chemistry of the azulenes has been the discovery of the large number and variety of condensation reactions that the system will undergo with aromatic and aliphatic aldehydes. Many similar reactions are undergone by indolizines and all these involve initial electrophilic attack.

Indolizines in the form of their salts react with 1-azulenyl, 3-indolyl and 1- and 3-indolizinyl aldehydes to form monomethine cyanine dyestuffs of types (XCIII) - (XCV)[2] analgous to those dyes in the azulene series such as (XCVI).[74] The structures of only a few of these products are known with certainty though the dyestuff from 3-formyl-2-methylindolizine and azulene is identical with that from 1-formylazulene and 2-methylindolizine (XCVII)-(IC) showing that in the latter case the 3-position of the indolizine is involved.

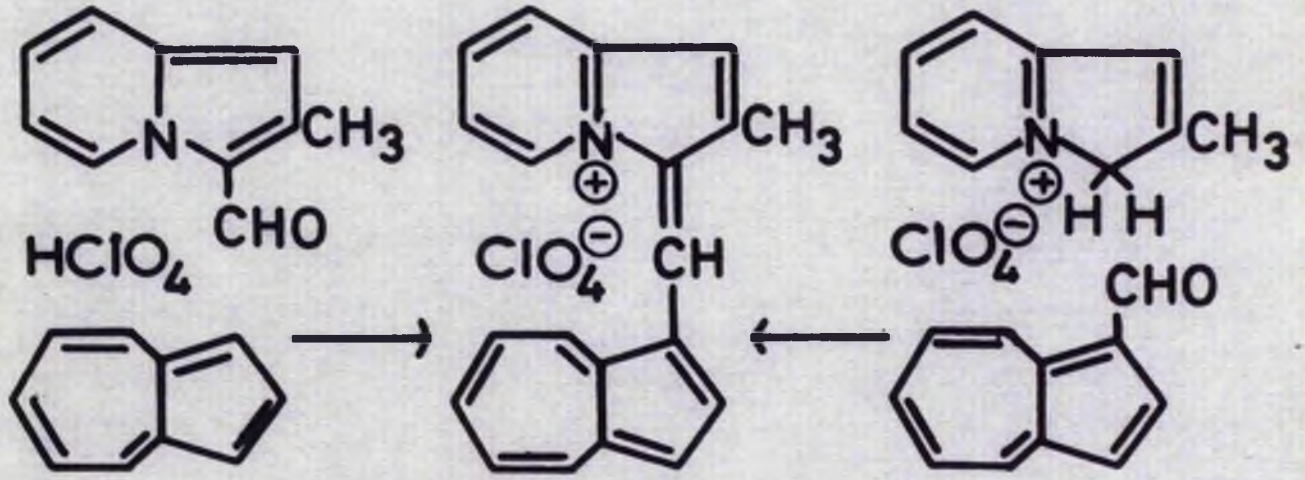
Similarly reaction of 1,2-dimethylindolizinium perchlorate with glyoxal affords a product (C) of similar nature and properties to that produced from 4,6,8-trimethylazulene and glyoxal in the presence of perchloric acid (CI).[75]

(7) Other reactions.

Halogenation and diazonium coupling reactions have received little attention and the results achieved are

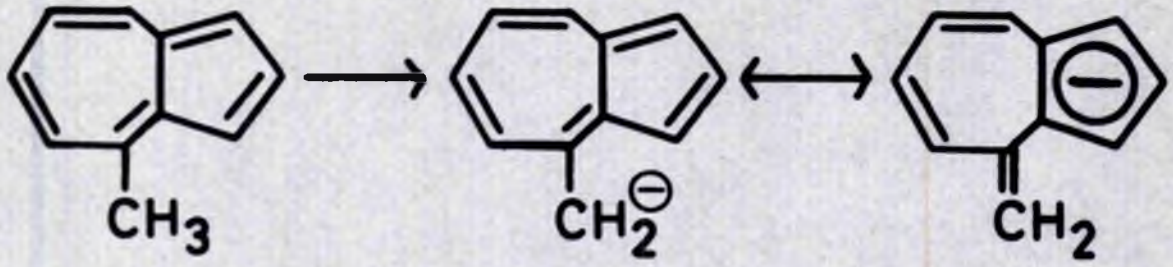


XCVI

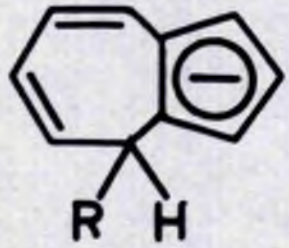


XCVII XCVIII IC

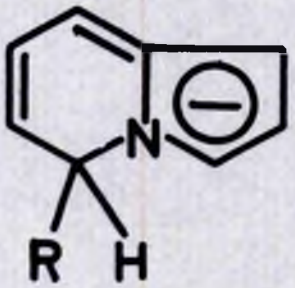
C CI



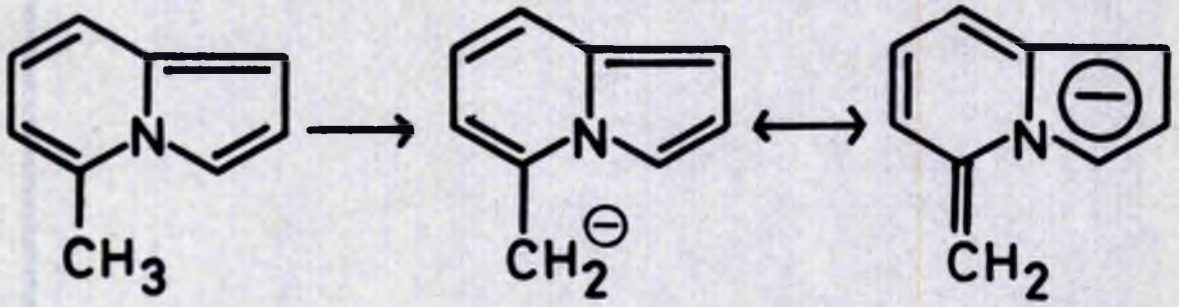
CII



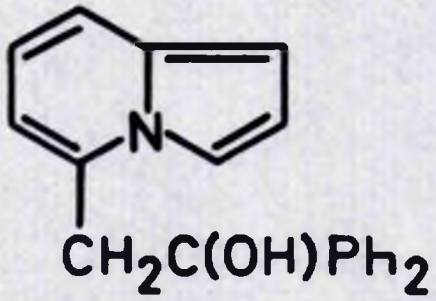
CIII



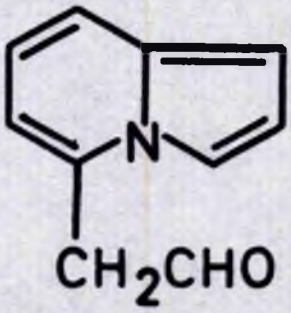
CVII



CIV



CV



CVI

of little value in a systematic examination of the reactions of indolizines.[76]

c) Nucleophilic attack.

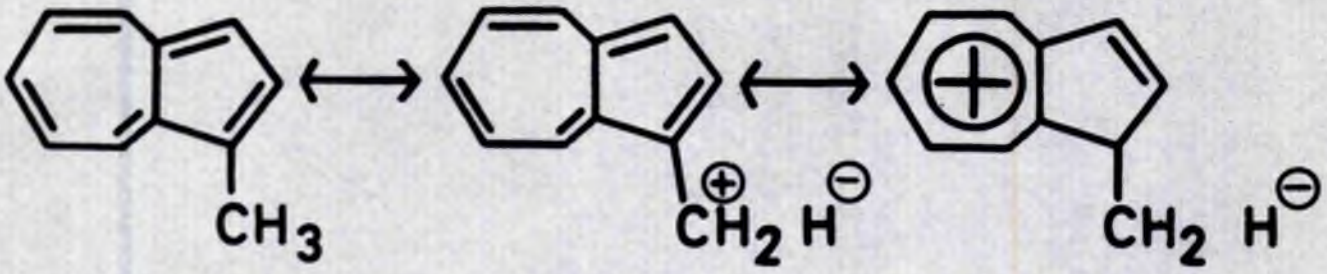
Only one attempt[14] has been made to subject indolizine to nucleophilic substitution. In the reaction of indolizine with sodamide no amino indolizine was isolated. Although no experimental details are available it is certain that this is an unfortunate choice of reagent in view of the difficulties involved in the isolation of 4-aminoazulene from a similar reaction. The application of methyl lithium, for example, might afford more definite results.

d) Properties of Substituents.

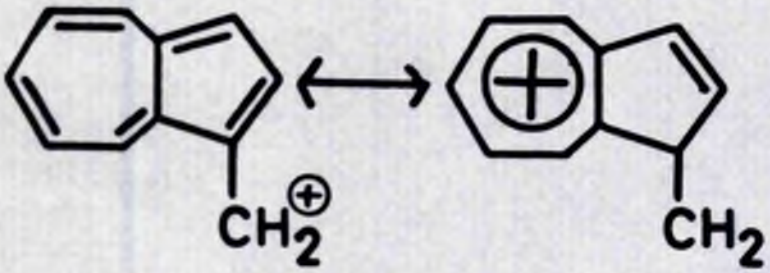
(1) Alkyl Groups.

Methyl groups attached to the 4(8)-position of an azulene nucleus are acidic and on treatment with a base such as lithium phenylmethyl amide afford anions of type (CII)[78,79] which are similar to the transition intermediates of nucleophilic substitution (CIII). The anion of (CII) undergoes the normal reactions of organo-lithium reagents and has been used to prepare a variety of azulene derivatives. Boekelheide[80,81] has shown that 5-methylindolizines react similarily with n-butyl lithium affording the anion (CIV) which with benzophenone affords the carbinol (CV) and with dimethylformamide gives the aldehyde (CVI). Again the similarity of (CIV) to the transition intermediate of nucleophilic substitution (CVII) is self evident.

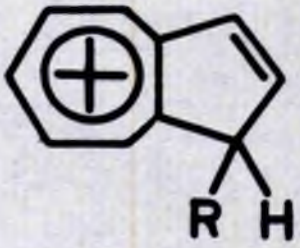
In contrast methyl groups at the 1(3) positions in azulene are basic as a result of "Hydride Hyperconjuga-



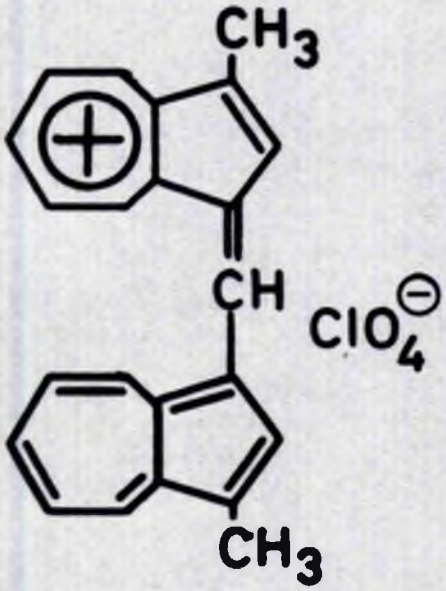
CVIII CVIII CVIIIb



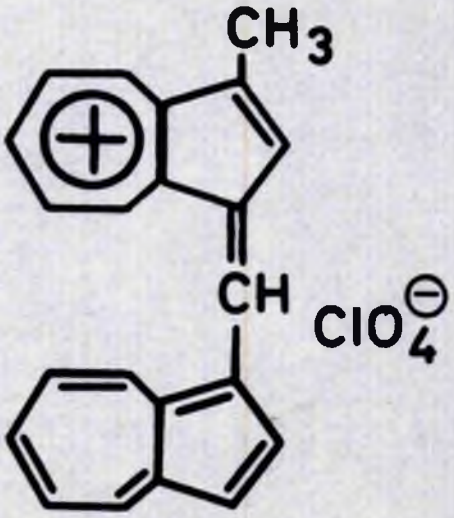
CX



CXIII



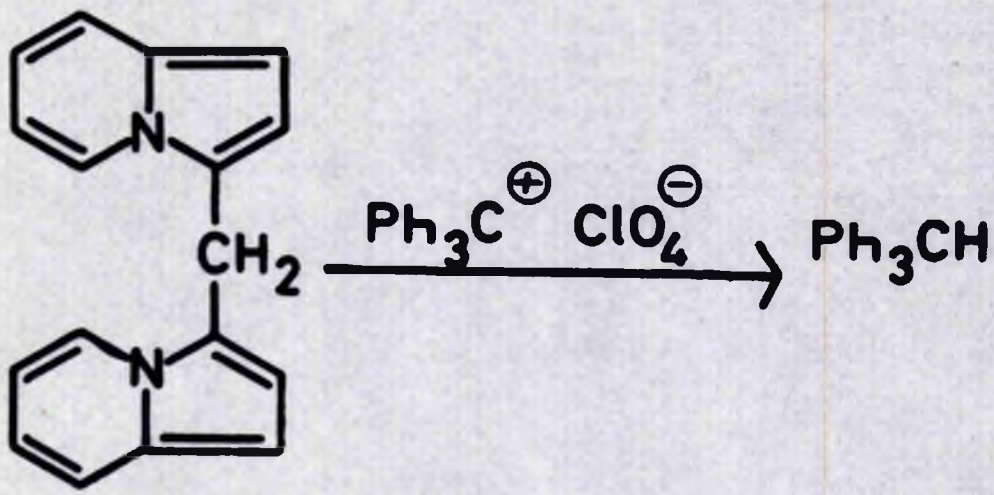
CXI



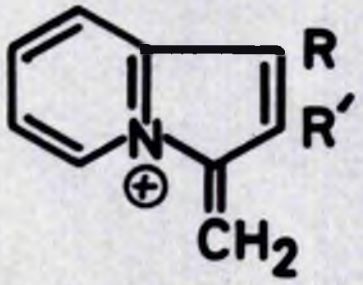
CXII

tion[82]" which may be described in terms of the theory of resonance as being due to the contribution of structures such as (CVIIIa) and (CVIIIb) to the ground state of 1-methylazulene (CVIII) with subsequent polarisation of the carbon-hydrogen bond. A hydride ion may be removed from such a group by a strong hydride acceptor such as the triphenylmethyl cation[82] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in the presence of perchloric acid[83] to afford the cation (CX). This cation, which is similar to the transition intermediate of electrophilic substitution (CXIII), undergoes a further sequence of reactions, the nature of which is as yet unknown, to give the monomethine cyanine dyestuffs (CXI) and (CXII) respectively.

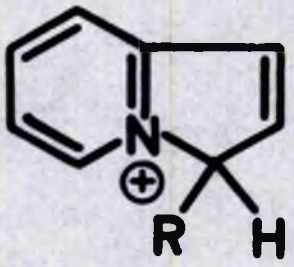
In the case of indolizines[2] the experimental evidence is not so definitive as in the case of azulenes. In their reaction with triphenylmethyl perchlorate, substitution, with the formation of trityl indolizines, takes place when either the 1- or the 3-position is unoccupied. Reaction of the methane (CXIV) with triphenylmethyl perchlorate, however, affords a quantitative yield of triphenylmethane, showing that hydride abstraction had taken place, but no other pure product could be isolated from the reaction. These phenomena are explained on the basis of the greater nucleophilicity of indolizines than azulenes. The reactions with quinones are also complicated by substitution reactions, 2,3-dimethyl-, and 1,2,3-trimethylindolizine affording 20% and 82% yields respectively of quinol on reaction with tetrachloro-1,2-benzoquinone, the other products being uncharacterisable. In spite of the scarcity of



CXIV



CXV



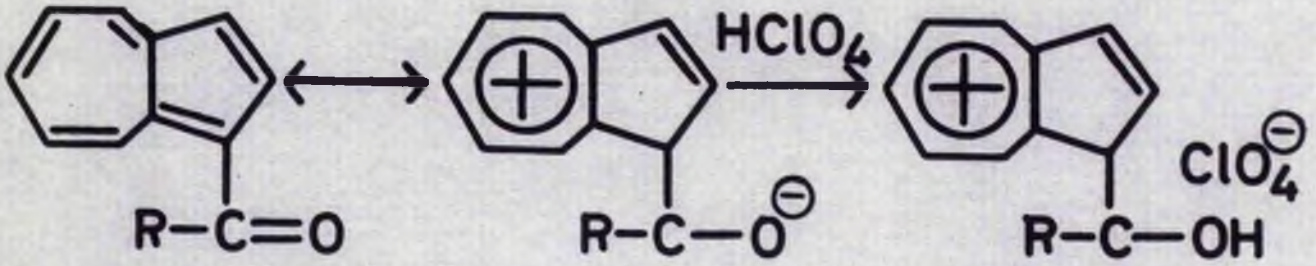
CXVI

evidence available it is quite clear that ions of type (CXV) are formed in these reactions affording an analogy both to the transition intermediates of electrophilic substitution in indolizines (CXVI) and to the behaviour of azulenes.

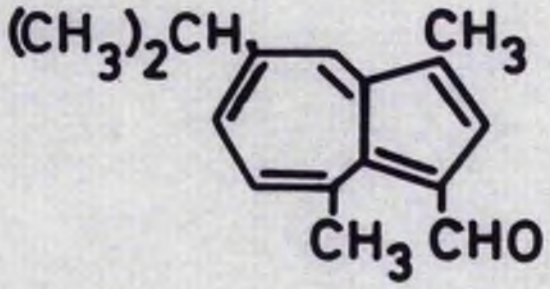
(2) Acyl Groups.

Owing to the ready polarisability of azulenes there is considerable interaction between the carbonyl group and the π-electron system of the nucleus in the 1(3)-acylazulenes. These compounds are best represented as resonance hybrids to which the polarised form (CXVIIb) makes significant contribution. The resulting degree of single bond character in the carbon-oxygen bond is reflected in the low infra-red carbonyl stretching frequencies[84], e.g., 1658cm^{-1} for 1-formylazulene as compared to 1700cm^{-1} for 1-napthaldehyde (both as solutions in carbon tetrachloride). This polarisation and the resulting lack of electrophilic character of the carbonyl carbon is also evident in the reactions of 1-formylazulenes. Treatment with strong acids such as perchloric acid affords stable crystalline salts of type (CXVIII)[85] and 1-formylazulene fails to undergo the Cannizzaro reaction, the benzoin condensation, and oxidation to the corresponding carboxylic acid.[86] Furthermore 3-formylguaiazulene (1-formyl-5-isopropyl-3,8-dimethylazulene) (CXIX) fails to react with grignard reagents, and is not reduced to an alcohol by lithium aluminium hydride.[87]

1-and 3-acylindolizines would also be expected to show considerable carbonyl polarisation due to the contribution of the resonance forms (CXXIa)and (CXXIb)



a CXVII b CXVIII



CXIX

a CXX b

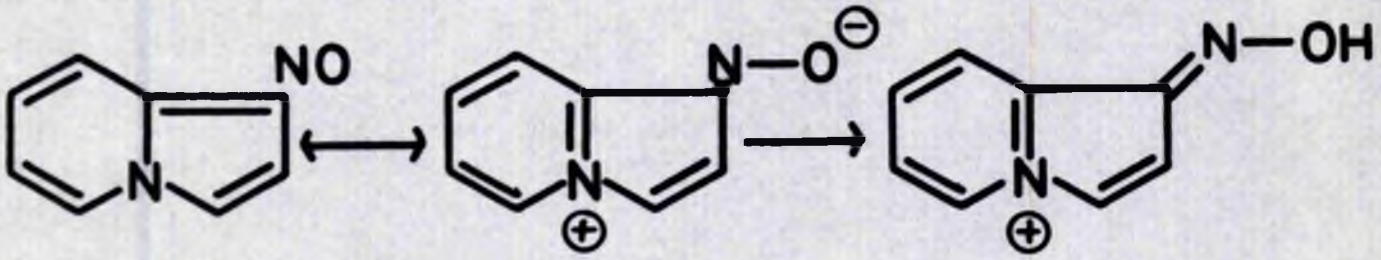
a CXXI b

respectively. Fraser[2] has measured the infra-red carbonyl stretching frequencies of a large number of indolizine aldehydes and has shown that these are abnormally low, e.g., 1637cm^{-1} for 3-formyl-2-methylindolizine (solution in carbon tetrachloride) and that the polarisation, as measured by the frequency in a given solvent, and the polarisability, measured as the difference in carbonyl stretching frequencies for two solvents[88] are greater in the more highly alkylated compounds and also in the case of the 3- than the 1-formylindolizines.

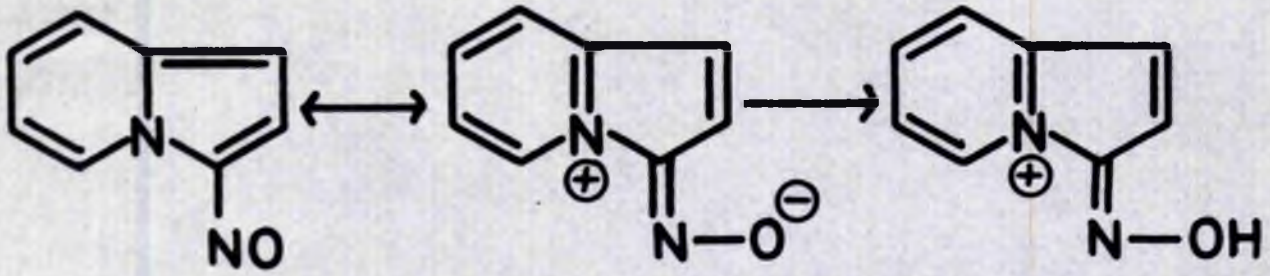
The abnormal polarisation is also reflected in the ease of reduction of 3-formylindolizines to the corresponding methyl compounds using lithium aluminium hydride either alone[65] or with aluminium chloride[2], the latter reaction having been developed as a general method for the de-oxygenation of polarised carbonyl groups.[89]

Most 3-acetylindolizines resist the formation of carbonyl derivatives such as oximes and phenylhydrazones, but 2,4-dinitrophenylhydrazones can be formed under forcing conditions.[16] The 1-acetyl compounds react normally[8,65] and, with 1,3-diacetyl compounds usually only the 1-acetyl group reacts.[11,16,65] Reaction of 3-acetyl-2-methylindolizine with grignard reagents affords mainly 2-methylindolizine[90] by an unknown mechanism but the reactions of 1,3-diacetylindolizine with methyl and phenyl grignard reagents proceeds normally at the 1-acetyl group.[8]

These results show a fair analogy between acylindolizines and acylazulenes, especially when the former



a *a* *a*



b *b* *b*

CXXII CXXIII CXXIV

are 3-substituted. The difference in behaviour of the 1-isomer is in agreement with the theoretical predictions discussed in section IIIa.

(3) Nitroso Groups.

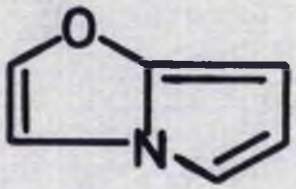
1 and 3 nitrosoindolizines (CXXII a and b)[26] are green in the solid state or when dissolved in non polar solvents. They are extremely soluble in water in which they form red solutions. This behaviour has been ascribed to the presence of the polarised forms (CXXIII a and b), and on the addition of acid yellow solutions containing the cations (CXXIV a and b) are formed.

e) Conclusions.

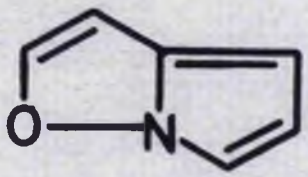
From the evidence presented above the analogy between the reactions of azulenes and indolizines is evident. The facts would seem to demonstrate a greater reactivity of indolizines towards electrophilic reagents but a reduced reactivity towards nucleophiles, although the latter reactions require systematic investigation. These facts are in agreement with a greater degree of ground state polarisation in indolizines, the bulk of positive charge being retained by the bridgehead nitrogen atom.

AIV. Heterocyclic analogues of indolizine.

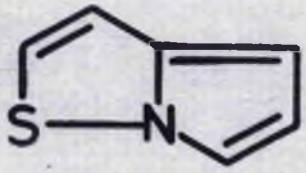
Of the six heterocyclic systems listed in section AI four are unknown except in some cases[76] as polyhydrogenated and oxygenated derivatives which are of little interest in the present context. These are pyrrolo[2,1-b]oxazole (CXXV), pyrrolo[1,2-b]isoxazole (CXXVI), pyrrolo[1,2-b]isothiazole (CXXVII), and pyrrolo [1,2-b]pyrazole (CXXVIII).



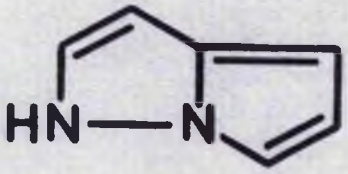
CXXV



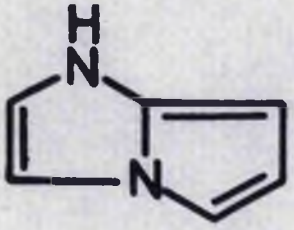
CXXVI



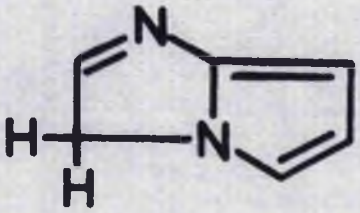
CXXVII



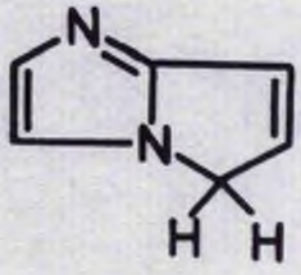
CXXVIII



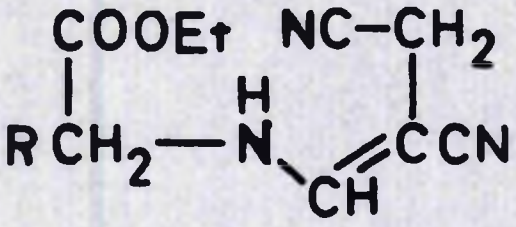
CXXIX



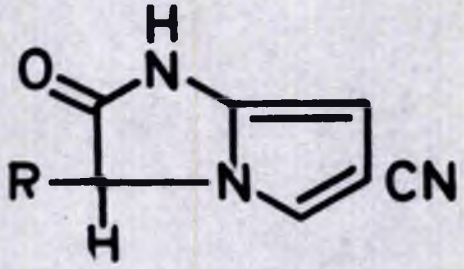
CXXIXa



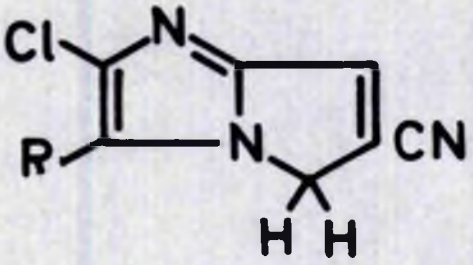
CXXIXb

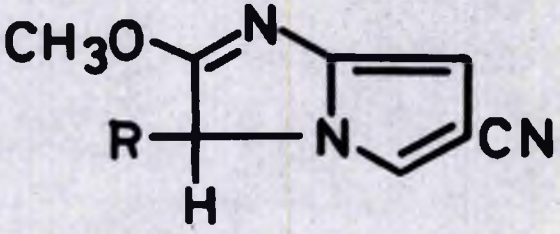


CXXX

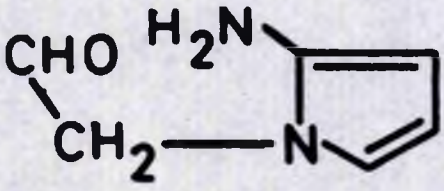


CXXXI





CXXXIII (R = H or CH_3) CXXXII



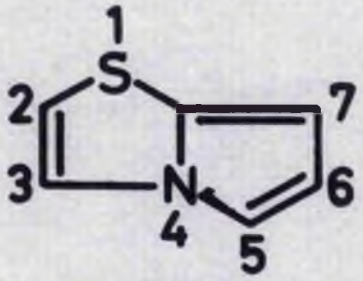
CXXXIV

Pyrrolo[2,1-a]imidazole (CXXIX)

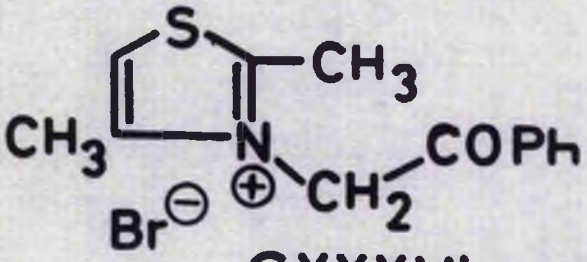
There is a possibility of tautomerism in this compound affording structures in which either a pyrrole (CXXIXa) or imidazole (CXXIXb) ring is completed and the limited amount of work that has been carried out on the system demonstrates that these are the favoured forms. Cyclisation of the compound (CXXX) using sodium ethoxide affords the lactam (CXXXI) which on treatment with diazomethane and with phosphorus oxychloride affords the pyrrolo[2,1-a]imidazole derivatives (CXXXII) and (CXXXIII) respectively.[91,92,93] The sole attempt[94] to prepare a simpler derivative, in fact the parent base, by the cyclisation of the pyrrole (CXXXIV) was unsuccessful.

Pyrrolo[2,1-b]thiazole (CXXXV).

The phenyl methyl derivative (CXXXVII) of this system was prepared[95] by cyclisation of the quaternary salt (CXXXVI) from 2,4-dimethylthiazole and phenacyl bromide, with aqueous sodium bicarbonate. The same method has been applied to the synthesis of the binuclear compounds (CXXXVIII)[96] and (CXXXIX)[97]. Since the completion of the synthetic work described in this thesis Kronkhe[98] has reported the preparation of the phenyl benzo derivative (CXLI) and its bromophenyl analogue, by the cyclisation of the salt (CXL) using methanolic triethylamine.



CXXXV



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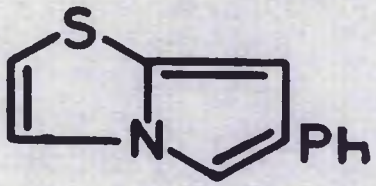

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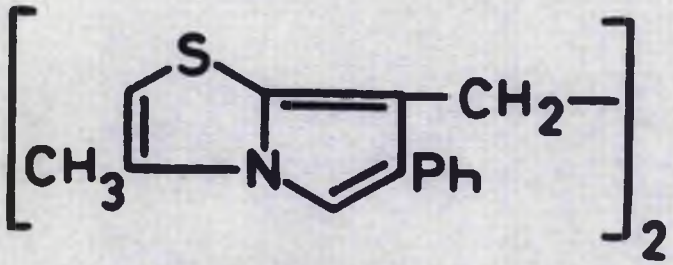
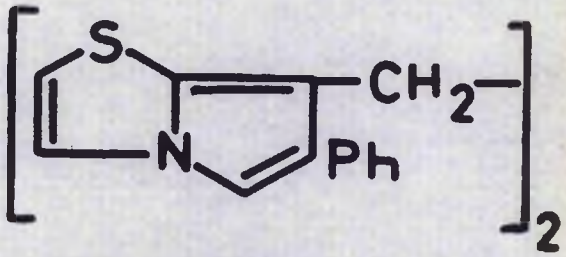
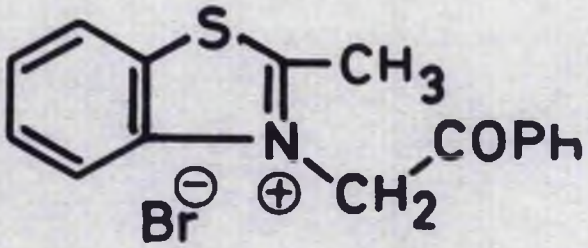


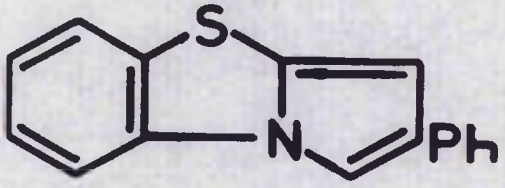
CXXXVIII



CXXXIX



CXL



CXLI

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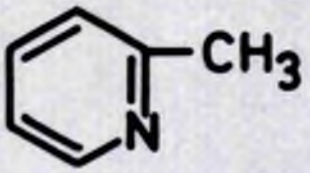
PART B

BI. Preparation of Thiazoles

Indolizines are readily formed from pyridines and analogously our main routes to the pyrrolo[2,1-b]thiazole series were based on the use of preformed thiazoles. Thiazoles prepared for this purpose were, (1)2-bromothiazole, (2)2-methylthiazole, (3)2-ethylthiazole, (4)2,4-dimethylthiazole, (5)2,5-dimethylthiazole, (6)2-ethyl-4-methylthiazole, (7)2-methyl-4-phenylthiazole, (8)2-benzyl-4-methylthiazole, (9)2-methyl-4,5-tetramethylenethiazole, and (10)2-methylbenzothiazole. With the exception of 2-bromothiazole and 2-methylbenzothiazole these compounds were prepared by the reaction of an α-halocarbonyl compound with a thioamide, the latter being either preformed or prepared insitu by the reaction of the corresponding amide with phosphorus pentasulphide according to the method of Hromatka[1] as developed by Kurkjy and Brown.[2] Application of the method of the latter workers to the synthesis of 2-ethylthiazole, 2-ethyl-4-methylthiazole, 2-methyl-4-phenylthiazole, 2-benzyl-4-methylthiazole, and 2-methyl-4,5-tetramethylenethiazole results in a greater yield of product and ease of preparation than afforded by existing literature methods.



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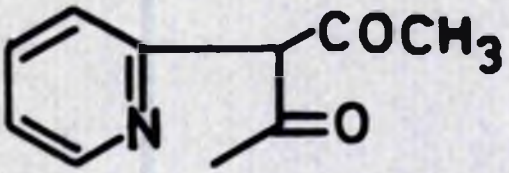

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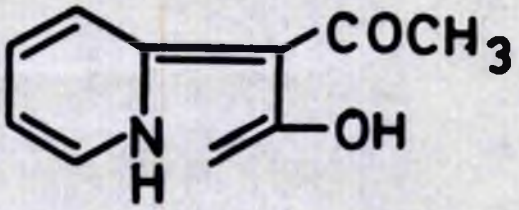

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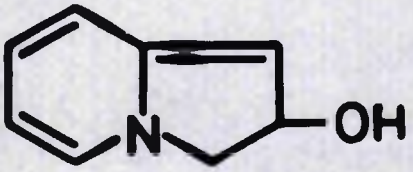

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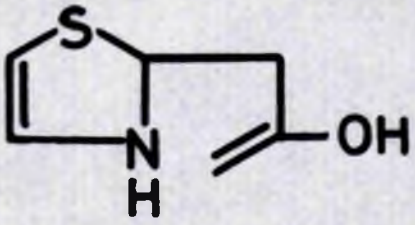


IV

BII. Synthesis of pyrrolo[2,1-b]thiazoles.

a) Attempted Scholtz synthesis of pyrrolo[2,1-b]thiazole.

As described in section AIIa the reaction of 2-picoline with acetic anhydride producing 1,3-diacetylindolizine is a convenient though low-yield route to indolizine. The analogous reaction using 2-methylthiazole was attempted but only traces of the required acetylpyrrolo[2,1-b]thiazoles were detected in the products. The mechanism proposed[3] to account for the formation of the indolizine derivative involves diacetylation of the 2-methyl group of the base (I) with subsequent cyclisation of the enolic form (IIb) of the resulting 1,3-diketone (II). Dehydration of the bicyclic product (III) and acetylation at the vacant 3-position follows. In considering the reasons for the failure of this reaction in the thiazole series two possibilities must be examined: a) the 2-methyl group in 2-methylthiazole may not be sufficiently reactive to allow an appreciable amount of diacetylation b) in the intermediate (IV) corresponding to (IIb) the nucleophilic character of the nitrogen atom may be reduced so that cyclisation does not take place to a significant extent. The latter is probably effective in preventing reaction occurring to any extent, due to the inductive electron attracting influence of the sulphur atom as displayed in the reduced basicity of thiazoles compared with pyridines.

b) Synthesis of pyrrolo[2,1-b]thiazoles by the Chichibabin reaction.

As this reaction consists of two separate stages, a) quaternisation of the appropriate thiazole with an α-halocarbonyl compound, and b) cyclisation of the resulting salt, these will be considered separately.

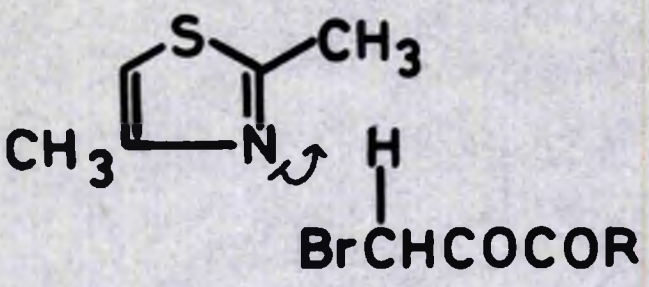
Quaternisation reactions.

We were concerned with the reaction of a variety of alkyl thiazoles with bromoacetone, phenacyl bromide and in a few cases only, methyl α-bromoethylketone, bromodiacetyl and ethyl bromopyrurate. Such quaternisation reactions in this series are unknown save for the reaction of phenacyl bromide with 2-methylbenzothiazole which has been realised[4] by reaction in boiling nitromethane. In the pyridine series it has been found[5] that such reactions are best accomplished using a solvent. This is usually acetone for the reactions with bromoacetone and ethanol for those with phenacyl bromide. The reactions are carried out at a variety of temperatures usually at the boiling point of the solvent. In the case of the less basic thiazoles we have found that quaternisations with phenacyl bromide are best achieved by prolonged refluxing in ethanol. The reactions with bromoacetone afforded optimum results when chloroform was the solvent either for a short period at the boiling point or for a prolonged period at room temperature. The latter condition generally afforded cleaner products.

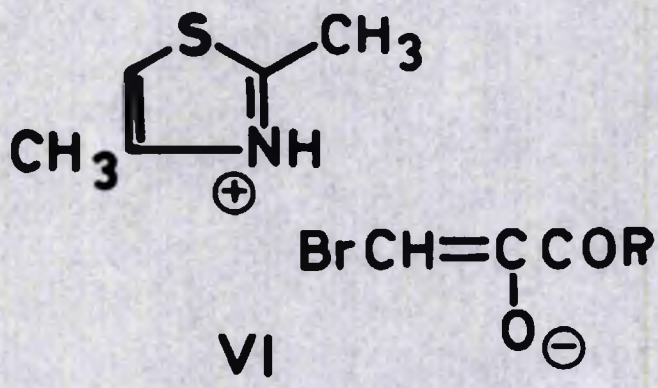
In certain cases it was found necessary to carry out the reaction by allowing an undiluted mixture of the

reactants to stand for a prolonged period at room temperature. In all cases the phenacyl bromides were stable, easily recrystallised, crystalline solids whereas the acetonyl quaternary salts, although usually crystalline, were sometimes hygroscopic and with the exception of the product from 2,4-dimethylthiazole could not be readily recrystallised. In such cases the bromides were converted, by treatment with perchloric acid in ethanol, into the more easily handled perchlorates which could be readily purified by recrystallisation and served to characterise the reaction products. In the single case of 3-acetonyl-2-ethyl-4-methylthiazolium the perchlorate was too soluble to be isolated and the picrate was utilised for characterisation.

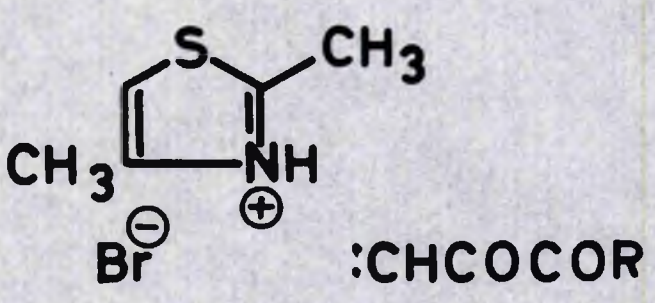
The reaction of methyl α-bromoethyl ketone was attempted with only 2-methyl-and 2-ethylthiazole. In the former case optimum results were obtained by heating an undiluted mixture of the reactants at 50°. It was not possible to isolate the crystalline quaternary thiazolium bromide, perchlorate or picrate from the reaction mixture and the crude product was submitted to our cyclisation procedure without further treatment. In the latter case reaction was achieved by refluxing in chloroform as solvent, affording a hygroscopic crystalline bromide which would not afford a crystalline perchlorate or picrate. It thus could not be purified and characterised and was therefore submitted directly to cyclisation. The results obtained with this haloketone are similar to those which have been encountered


S
CH3
CH3
N
H
BrCHCOCOR

V


S
CH3
CH3
NH
BrCH=C COR
O

VI


S
CH3
CH3
NH
Br
:CHCOCOR

VII

in its applications to indolizine syntheses and are presumably due to the ease of elimination of hydrogen bromide from the molecule with consequent contamination of the products by thiazolium hydrobromides.

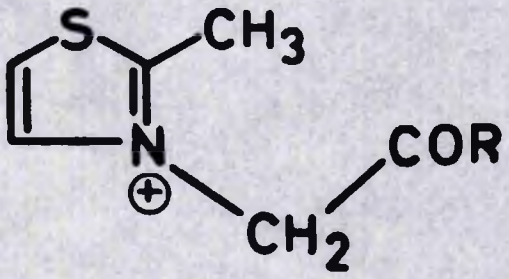
Quaternisation reactions with bromodiacetyl and ethyl bromopyrurate have received little previous consideration. The latter, as described in section AIIb, has been caused to react with several pyridines by prolonged reaction in ethanol, no solid quaternary salts, being isolated, and the residue after removal of solvent was utilised in further reactions. In our trial reactions of these compounds using 2,4-dimethyl thiazole the reactions were attempted in a variety of solvents, i.e., alcohols, ethers, ketones, esters, and halogenated hydrocarbons, and under a variety of conditions. In no case could a solid quaternary thiazolium salt be isolated. Reaction without a solvent resulted in a violently exothermic reaction with much decomposition. The most curious feature of these experiments is that in ether a rapid and almost quantitative precipitation of thiazolium hydrobromide occurred due possibly to initial proton abstraction from the ketone by base with subsequent loss of a bromide ion resulting in a carbene type intermediate (V-VII R:CH_3- or C_2H_5O-), a reaction which deserves further study. The preparation of the quaternary salts was achieved in the case of bromodiacetyl by reaction in chloroform over a prolonged period, the quaternary salt being subsequently extracted into water for cyclisation. In the case of ethyl bromopyruvate the method of Borrows and Holland[6] was utilised,

i.e., reaction in ethanol followed by removal of solvent and cyclisation of the cryde residue.

Cyclisation

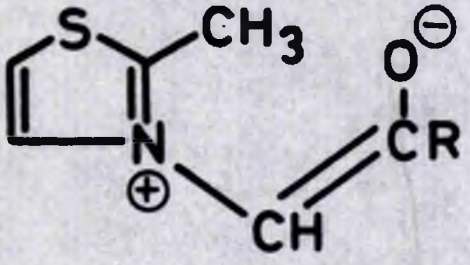
As described in section AIV some substituted 6-phenylpyrrolo[2,1-b]thiazoles have been prepared by cyclisation of the corresponding phenacylthiazolium salts with aqueous bicarbonate and in the single case of 6-phenylbenzo[b]pyrrolo[2,1-b]thiazole using methanolic triethylamine. We have repeated the preparation of 3-methyl-6-phenylpyrrolo[2,1-b]thiazole[7] and have carried out the preparation of 6-phenylbenzo[b]pyrrolo[2,1-b]thiazole utilising aqueous bicarbonate. In both cases the yields were low and the products extremely impure.

In our attempt to prepare simpler derivatives of pyrrolo[2,1-b]thiazole we selected for preliminary examination the cyclisation of 2-methyl-3-phenacylthiazolium bromide and 3-acetonyl-2-methylthiazolium bromide to 6-phenyl-, and 6-methylpyrrolo[2,1-b]thiazole respectively. The former salt on treatment with a variety of aqueous bases, i.e., hydroxide, carbonate, bicarbonate, and acetate, afforded a solid material containing only traces of 6-phenylpyrrolo[2,1-b]thiazole as detected by Ehrlich's reagent, a sensitive reagent for detecting the presence of a pyrrolo ring. The bulk of the product appeared to consist of a polymer of fairly low molecular weight. Attempted cyclisation of the acetonyl quaternary thiazolium salt using the same reagents with isolation of the product by steam distillation afforded a large quantity of presumably polymeric steam-involatile material while the distillate contained only traces of material affording a positive test



VIII

BASE.



IX

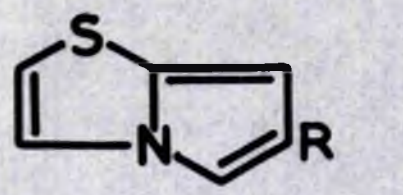
with Ehrlich's reagent.

We found that cyclisation could be readily effected under aprotic conditions by treating the quaternary salt with two equivalents of sodium acetate as base in boiling acetic anhydride. The pyrrolo[2,1-b]thiazole produced undergoes acetylation by the acetic anhydride but the acetyl groups are readily removed subsequently by acid hydrolysis. This will be discussed later. The degree of acetylation is dependent on the extent and nature of the substitution of the ring system. We consider that this reaction is practically quantitative, the low yields of certain pyrrolo[2,1-b]thiazoles after hydrolysis being due to side reactions in the latter step which will be discussed below. The nature of the anion of the quaternary salt seems to influence the nature of the products. Thus cyclisation of 3-acetonyl-2-methylthiazolium perchlorate afforded a product containing more diacetyl-6-methylpyrrolo[2,1-b]thiazole than is obtained from the corresponding bromide. Presumably this is due to the fact that perchloric acid is a stronger acid than hydrobromic and hence is a more effective acetylation catalyst.

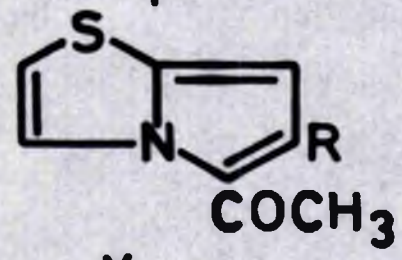
The failure to cyclise the quaternary salts in aqueous media and the success of the somewhat unusual method described above is difficult to rationalise. One possible explanation is that the enol-betaine intermediate in the cyclisations (IX R=Me- or Ph-) is unstable in aqueous media or might be destroyed by strong bases. The latter is more likely as sodium acetate in acetic

anhydride would be a very weak base. Furthermore Skelton[8] has attempted the cyclisation of the same two quaternary salts using potassium tertbutoxide and sodium acetate in dimethyl sulphoxide, and triethylamine, potassium cyanide, lithium and sodium acetates in dimethylformamide. All of these methods afforded only traces of cyclised material save the last two which gave about 5% yields of the 6-methyl- and 6-phenylpyrrolo-[2,1-b]thiazoles. The successful cyclisations by aqueous base of the substituted compounds as described in section AIV could be due to the nature and position of the substituent groups preventing decomposition or(e) some other side reaction.

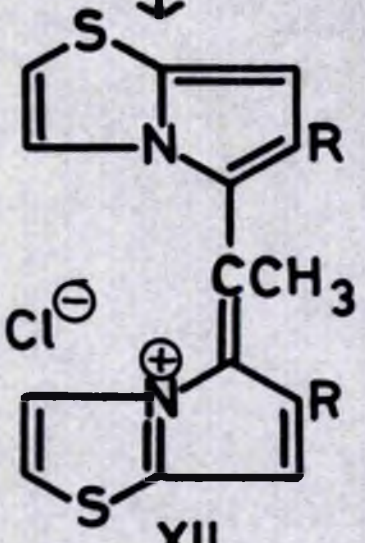
We have applied the method to the preparation of the following substituted pyrrolo[2,1-b]thiazoles: (1)6- methyl-, (2)6-phenyl-, (3)2,6-dimethyl-, (4)3,6-dimethyl-, (5)5,6-dimethyl-, (6)6,7-dimethyl-, (7)2-methyl-6-phenyl-, (8)3,6,7-trimethyl-, (9)5,6,7-trimethyl-, (10)6-phenylbenzo[b]-, (11)3,6-dimethyl-7-phenyl-, (12)6-methyl-2,3-tetramethylene-, (13)6-phenyl-2,3-tetramethylenepyrrolo[2,1-b]thiazole. In the case of 5,6,7-trimethylpyrrolo[2,1-b]thiazole the product isolated was the base but in all other cases acetylated products were formed. The method seems to be fairly general and can be applied to fairly impure samples of quaternary thiazolium salts. Thus in the preparation of 5,6-dimethylpyrrolo[2,1-b]thiazole the entire product from the reaction of undiluted 2-methylthiazole and methyl α-bromoethyl ketone was subjected to cyclisation, the impurities being subsequently removed after hydrolysis of the acetylated product.



XI



X



XII

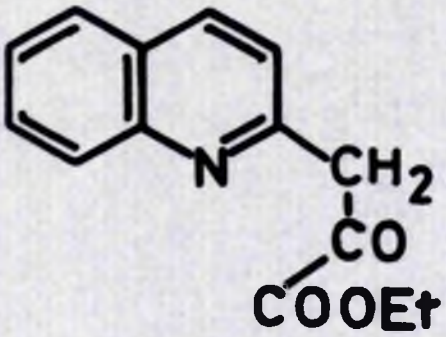
The deacetylation is the most critical stage of this method of synthesis and a variety of reagents were employed. This is due to the possibility of two types of reaction: (1) hydrolytic deacetylation of the acetyl compound (X) affording the base (XI), (2) condensation of the acetyl compound with the free base leading to the formation of a monomethine cyanine dyestuff (XII). The reagent used for this hydrolysis has in all cases been hydrochloric acid, either concentrated or diluted with water. Dioxane or acetic acid was added to facilitate solution of the acetylated material. Higher acid concentrations tend to cause dyestuff formation to occur to a greater extent and as such concentrations are necessary to effect the cleavage of diacetyl compounds and of those monoacetyl compounds with electron attracting substituents such as phenyl, the nature of the hydrolysis mixture is extremely critical and the yields are generally low in such cases. No doubt the yields in some cases could be improved by a careful study of the hydrolysis conditions.

The cyclisation of the products from 2,4-dimethylthiazole with bromodiacetyl and ethyl bromopyrurate could not be accomplished by this method as it was only possible to form the quaternary salts in chloroform and ethanol solutions respectively. In the first case the salt was extracted into aqueous solution and cyclised with sodium bicarbonate producing 6-acetyl-3-methylpyrrolo[2,1-b]thiazole in low yield together with a large quantity of tarry by-products. However the product was preferentially extracted by ether and purified in the normal manner. In the latter case the procedure

of Borrows and Holland[6] for the corresponding 2-picoline case was followed exactly. Only a small quantity of product was obtained after esterification and distillation of the crude 3-methylpyrrolo[2,1-b]thiazole-6-carboxylic acid and this was found to be a mixture. It had been hoped that these two reactions might afford a possible synthesis of pyrrolo[2,1-b]thiazoles unsubstituted in the pyrrole ring by oxidation of the former to the latter and decarboxylation. However, the poor yields in the case of 2,4-dimethylthiazole and the difficulty in obtaining the large quantities of 2-methylthiazole that would be necessary for the preparation of the parent base led to the abandonment of the method.

c) Synthesis of pyrrolo[2,1-b]thiazole from substituted 2-n propylthiazoles.

Although the Chichibabin method allowed us to prepare a large variety of substituted pyrrolo[2,1-b]-thiazoles the synthesis had the disadvantage that it could not be applied to pyrrolo[2,1-b]thiazoles unsubstituted in the 6-position including the parent base. Accordingly we turned our attention to the possibility of forming the pyrrole ring by the intramolecular cyclisation of a suitable three carbon side chain at the 2-position of a thiazole. Analogous methods which have been successfully applied to the indolizine series are described in section AIIe. The majority of these methods employ pyrolytic or dehydrogenative cyclisations and are clearly not applicable in the case of pyrrolo-[2,1-b]thiazoles in view of the presence of the sulphur atom of a thiazole. The compounds required should be capable of cyclisation under fairly mild conditions and hence there are two necessary structural features of the side chain: a) it must carry a suitable group in the terminal 3-position in order to allow reaction at the nitrogen atom and initial ring closure, b) it must carry a further substituent which may be eliminated to allow the correct oxidation level of the pyrrolo[2,1-b]thiazole to be realised after cyclisation. The former can be achieved by any group which is capable of undergoing nucleophilic displacement by nitrogen, such as halogen or certain ester groupings, and the latter by any group capable of olefin-forming elimination and situated at either the 1- or the 2-position. The driving force



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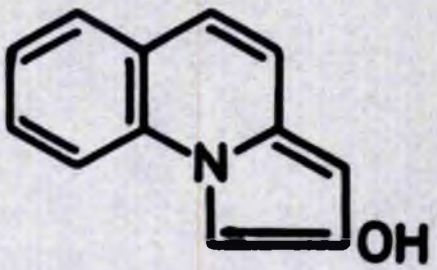
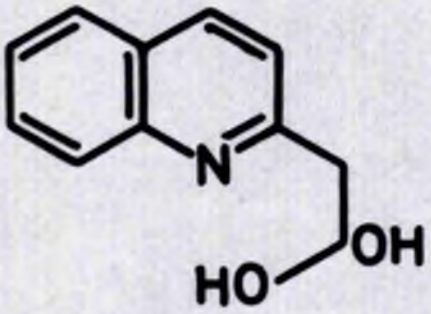
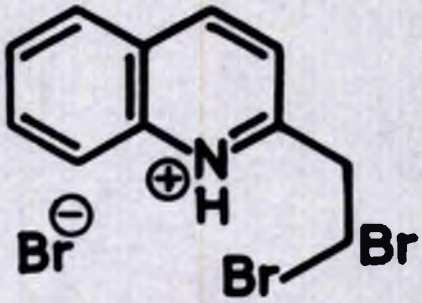


XX



XIV



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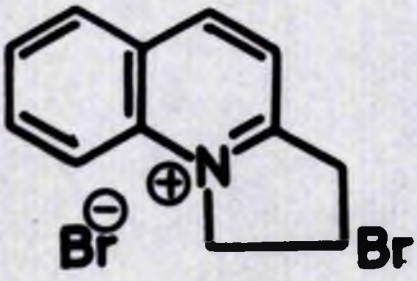
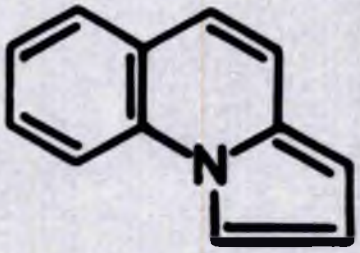


XVI

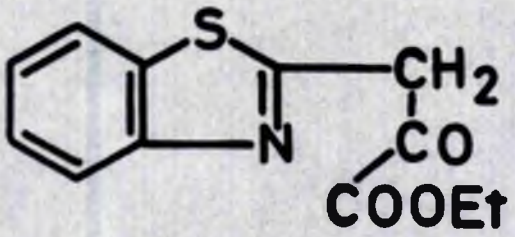


XVII

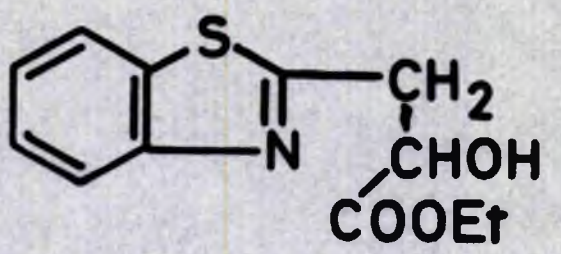
for the elimination would be large in view of the consequent formation of the aromatic bicyclic system and the nature of the group should not be over-critical.

In our first approach we attempted to make use of the method developed by Boekelheide[9] for the synthesis of benzo[e]indolizine. Reduction of ethyl 2-quinolylpyrurate (XIII) with sodium borohydride afforded the diol (XIV), treatment of this compound with hydrobromic acid produced the dibromo compound (XV), and this was cyclised with alkali, presumably via the quaternary (XVI) to the indolizine (XVII). The corresponding ethyl 2-benzothiazolylpyrurate (XVIII) is known and is readily prepared in quantity from 2-methylbenzothiazole and diethyl oxalate. In an attempt to utilise a simpler system we attempted the condensation of 2-methyl-4-phenylthiazole with diethyl oxalate using potassium ethoxide in ether-ethanol and potassium tertbutoxide in benzene as catalysts. In both cases condensation failed to occur. This result can be ascribed to a lower acidity of the methyl group in 2-methyl-4-phenylthiazole, due presumably to a lower degree of resonance stabilisation of the anion resulting from proton loss.

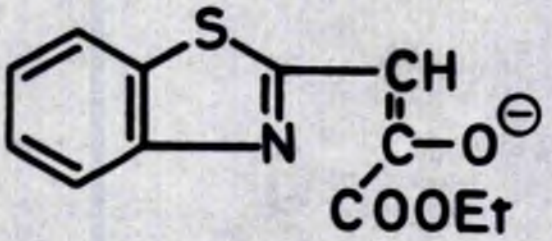
Accordingly our experiments were limited to ethyl 2-benzothiazolylpyrurate (XVIII). In the case of the quinoline compound (XIII) reduction to the diol was effected by theaction of methanolic sodium borohydride on the potassium enolate, probably the only instance of the reduction of an ester by this reagent. Application of this procedure in our case resulted in the isolation of only starting material while reaction of the ester



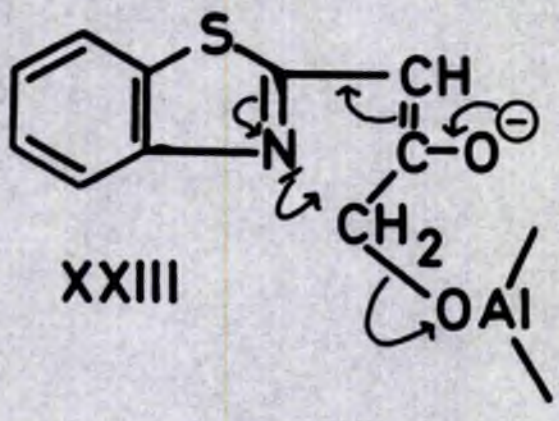
XVIII



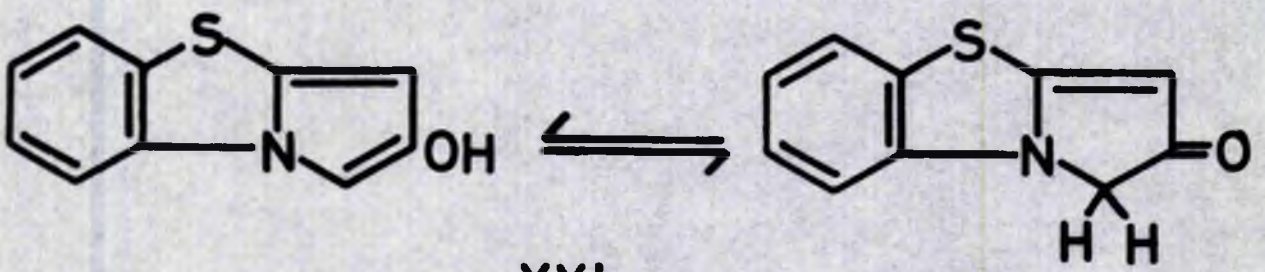
XIX



XXII



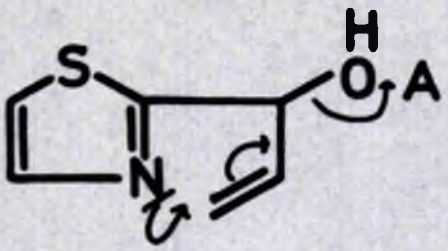
XXIII



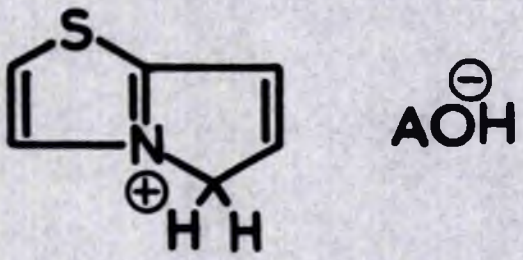
XXI

itself afforded a thermally unstable product which could not be purified for characterisation but whose infra-red spectrum indicated that it was ethyl 2-(2-benzothiazolyl)lactate (XIX).. The reasons for this difference in behaviour between the thiazole and pyridine series are as difficult to understand as the reasons for the success of the method in the quinoline case. We next attempted to carry out the reduction using lithium aluminium hydride in tetrahydrofuran. In a similar reduction of the quinoline analogue Boekelheide obtained a product to which he assigned structure (XX). The product in our case could not be purified satisfactorily for characterisation but seems to be (XXI) analagous to (XX) since it affords colour reactions with ferric chloride and Ehrlichs reagent, properties of (XX). This product is probably formed by the route (XVIII) - (XXII) - (XXIII) - (XXI), reaction of the ester (XVIII) with the hydride affording the enolate (XXII) which is reduced to (XXIII) and cyclises to (XXI).

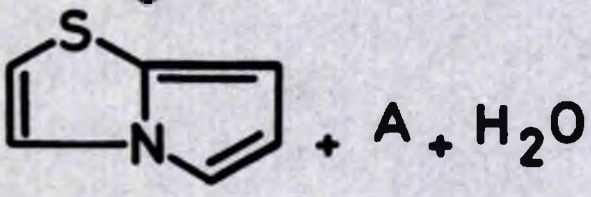
In view of the failure ofthe approach described above we turned our attention to other methods of forming a thiazole with a suitably substituted side chain. A method which has had considerable success in indolizine chemistry uses 2-pyridyl lithiums which form the basis of Barrets method of synthesis (see section AIIc). Although knowledge of the 2-thiazolyl lithiums is not nearly so well developed as in the pyridine case some information is available. Gilman[1] has prepared 2-benzothiazolyl lithium by the reaction of benzothiazole with butyl lithium; the yield is 90% as measured by carbonation, and the reagent reacts well



XXIV



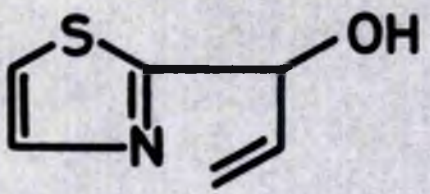
XXV



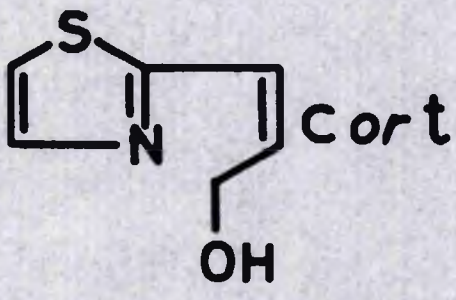
XXVI

with nitriles and ketones. Breslow[11] has achieved the same type of exchange with 4-methylthiazole at reduced temperature, the reagent reacted with acetaldehyde to afford the required carbinol in 40% yield. The work most relevant to our needs however is that of Kurkjy and Brown[12] who prepared 2-thiazolyl lithium from 2-bromothiazole by halogen-metal exchange at -30°, reaction with benzaldehyde affording the appropriate carbinol in 90% yield. Furthermore the same workers were able to prepare thiazolyl magnesium bromide from the same halide utilising the entrainment method[13] with ethyl bromide. In view of the ease of preparation of 2-bromothiazole from the commercially available 2-aminothiazole these two reagents were utilised in the whole of this work.

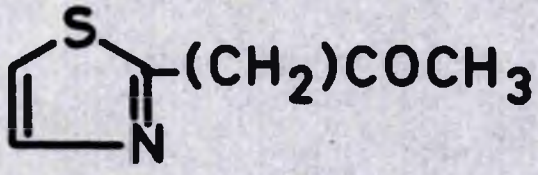
In the initial experiments we attempted to synthesise some 2-thiazolyl vinyl carbinols of type (XXIV) in the hope that these could be cyclised to pyrrolo[2,1-b]thiazoles by the action of a mild eletrophile according to the mechanism (XXIV) - (XXVI) which resembles that for the prototropic rearrangement of phenyl vinyl carbinols.[14] The carbinols were produced from the organometallics and $\alpha\beta$-unsaturated aldehydes and ketones. In the first attempt acrolein was used in the hope of obtaining the parent base. The reaction produced large quantities of polymeric material even when no excess of the aldehyde was used and a low yield of the carbinol was obtained which was examined by gas-liquid chromatography. This showed that the product was a mixture of substances with close boiling points presumably the desired product (XXVII) together with the two stereo-



XXVII



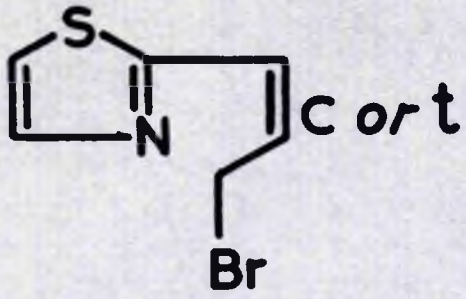
XXVIII



XXIX

isomeric forms of the isomeric alcohol (XXVIII). Replacement of the acrolein by methyl vinyl ketone afforded mainly a carbonyl compound as product together with a small quantity of carbinol material. The latter was a mixture as before and the former presumable is the ketone (XXIX) formed by 1,4 addition of the organometallic reagent to the ketone. Reaction of crotonaldehyde with thiazolyl magnesium bromide gave again a mixture of isomeric carbinols of similar volatility probably due to rearrangement during work up, the driving force for the conversion of (XXVII) into (XXVIII) is quite large as the degree of conjugation in the molecule is being increased.

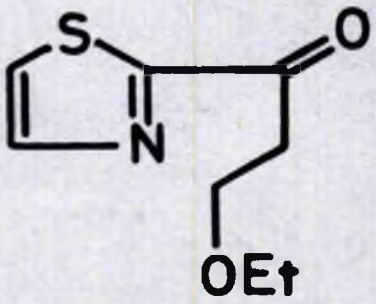
Attempts were made to cyclise the crude carbinols obtained as described above by the action of a variety of reagents: a)0.5N sulphuric acid, b)0.05N sulphuric acid, c)glacial acetic acid, d)acetic anhydride, e) 9N hydrobromic acid followed by alkali, f)48% hydrogen bromide in acetic acid followed by alkali. In the first four cases it was hoped that cyclisation would occur by the mechanism previously advanced and in the last two cases by conversion of the carbinols into alkyl bromides of type (XXX). In each case traces of pyrrolo[2,1-b]thiazoles as detected by Ehrlichs reagent were produced but in no case was sufficient present to allow isolation even as a derivative. This is presumably due, in the cases of cyclisation by a mild electrophile, to preferential attack at nitrogen and in the attempted cyclisations via the bromo compounds of type (XXX) to unfavourable stereochemistry as the double



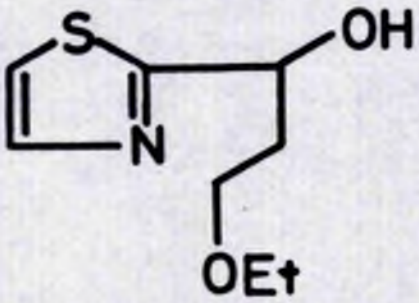
XXX

$EtOCH_2CH_2CN$

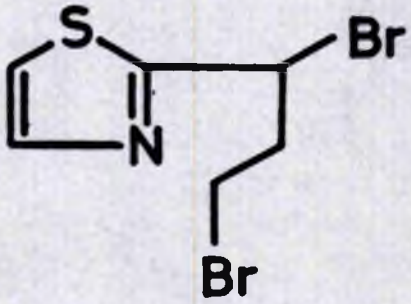
XXXI



XXXII



XXXIII



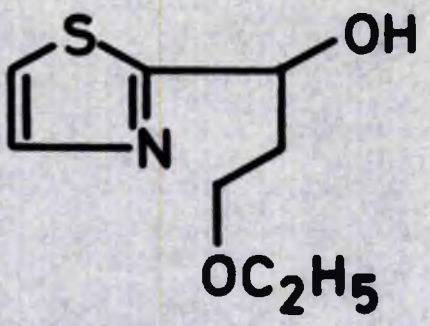
XXXIV

bond migration leading to (XXX) would produce the more stable trans isomer.

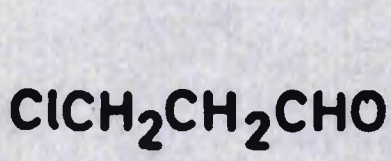
The next approach was aimed at the preparation of the dibromo compound (XXXIV). We hoped by the reaction of the 2-thiazolyl-metal compound with 3-ethoxypropionitrile (XXXI) to obtain the ethoxyketone (XXII) which would be reduced to the alcohol (XXIII) by sodium borohydride or a similar reagent and on treatment with hydrobromic acid this would afford the dibromo compound (XXXIV) which should be capable of cyclisation with alkali. In the reaction with 2-thiazolyl lithium the only product isolated was a trace of an aliphatic ketone whose volatility indicated that it was the product of reaction of the nitrile with the excess of nbutyl lithium used in the formation of the 2-thiazolyl lithium. The product also contained a large quantity of a red gum. Use of 2-thiazolyl magnesium bromide again afforded none of the required ketone. The only material isolated was the ketone produced by the reaction of the nitrile with the ethyl magnesium bromide present along with the 2-thiazolyl magnesium bromide as a result of the use of the entrainment method for the preparation of the latter.

Attention was then turned to the use of the two analogous compounds 3-ethoxypropionaldehyde (XXXV) and 3-chloropropionaldehyde (XXXVI). These with 2-thiazolyl metal compounds would afford the 1,3 disubstituted compounds (XXXVII) and (XXVIII) respectively. The former is one of the intermediates envisaged in the approach from 3-ethoxypropionitrile and the latter which has the

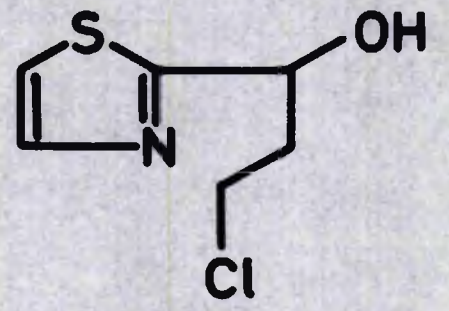
XXXV



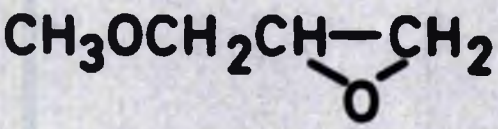
XXXVII



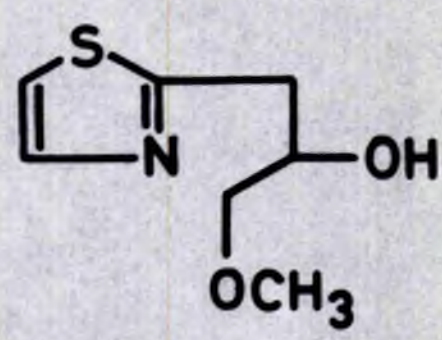
XXXVI



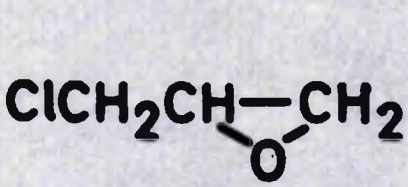
XXXVIII



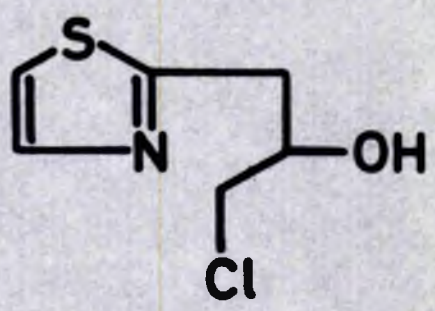
XXXIX



XLI



XL



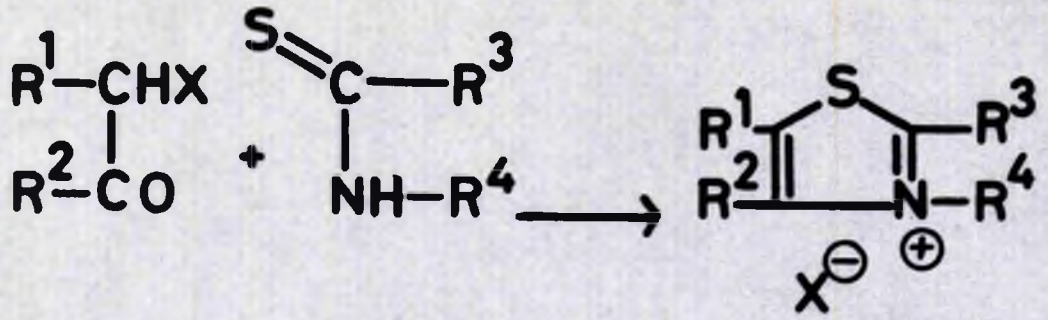
XLII

same oxidation level should be capable of direct cyclisation. In the first case reaction with 2-thiazolyl lithium took place smoothly andafforded the required product in good yield. Attempts were made to cyclise the compound by treatment with concentrated hydrobromic acid or with hydrogen bromide in acetic acid followed in each case by treatment with alkali. In both approaches traces of pyrrolo[2,1-b]thiazole, as detected by Ehrlichs reagent, were formed but an insufficient quantity was present to permit isolation even as a picrate or perchlorate. The reaction of the chloroaldehyde with 2-thiazolyl lithium was carried out but in this case, as would be expected on the basis of its structure, the product was thermally unstable and could not be purified for characterisation. Cyclisation by a variety of reagents was attempted: a)concentrated hydrobromic acid followed by alkali, b)boiling ethanol, c)boiling tertbutanol, d)boiling acetic acid, e)formamide at 100°. However in each case only traces of ring-closed material could be detected in the product.

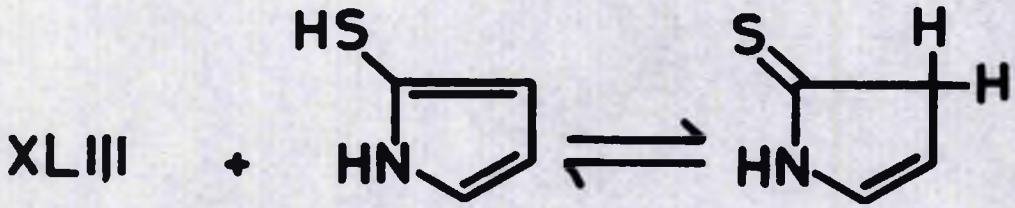
In view of the possibility that the 1,3 disubstituted compounds might not be satisfactory due to some interaction of the 1-substituent with the aromatic nucleus we next attempted to use the analogous 2,3-disubstituted compounds (XLI) and (XLII) obtained from 3-methoxy-poxypropane (XXXIX) and epichlorohydrin (XL) respectively. In the reaction of 2-thiazolyl lithium with 3-methoxyepoxypropane only a trace of the required methoxy alcohol in a fairly impure state was obtained, together with the product from the reaction of the epoxide with the excess of butyl lithium as in previous

cases. The amount of the substituted thiazole obtained was insufficient to merit purification for characterisation and the whole of the material was subjected to an attempted cyclisation with hydrobromic acid followed by alkali. Only traces of pyrrolo[2,1-b]thiazole were detected in the product using Ehrlichs reagent. Reaction of epichlorohydrin with 2-thiazolyl lithium afforded a thermally unstable material which could not be purified. Attempts were made to cyclise this material using a variety of reagents and optimum results were obtained by refluxing in tert butanol when pyrrolo-[2,1-b]thiazole was produced in 1.9% yield.

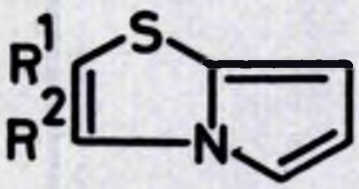
These results demonstrate that 2-thiazolyl lithium is a fairly unreactive species, failing to react to any significant extent with nitriles and epoxides at temperatures below -10° above which temperature it decomposes to the red polymeric gum encountered in so many of these reactions. This low extent of reaction explains the poor yield obtained in the only successful synthesis of this series. The failure to cyclise the products from 2-thiazolyl lithium with 3-ethoxypropionaldehyde and 3-methoxyepoxypropane must presumably be due to preferential intermolecular reaction and in the case of 3-chloropropionaldehyde may be complicated by more complex reactions with the organometallic reagent possibly involving reaction of the chlorine atom.



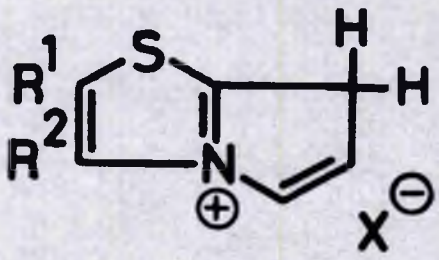
XLIII XLIV XLV



XLVI



XLVIII



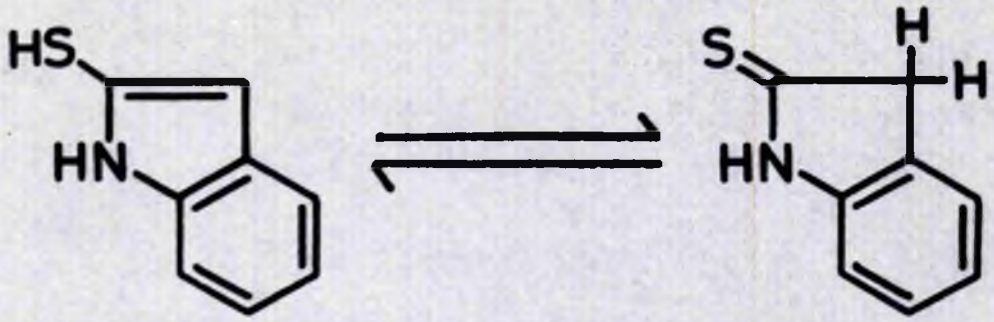
XLVII

d) Syntheses of pyrrolo[2,1-b]thiazoles involving closure of the thiazole ring.

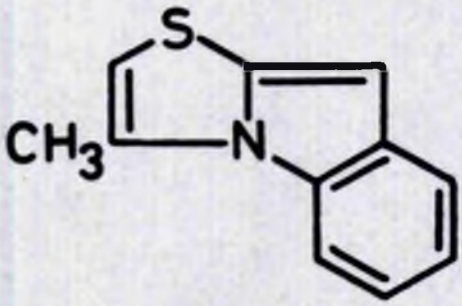
The syntheses described above are all based on methods which have been successfully applied to the formation of indolizines from pyridine derivatives. Two possible approaches have been omitted: a) the Barret synthesis since it does not provide a route to the parent base, which was our main interest outside the products from the Chichibabin reaction, b) the syntheses utilising acetylenic esters which is a fairly complex reaction and produces a variety of quinolizine compounds which are outside the scope of this work.

One possible route remains that in which a thiazole ring is built onto a preformed pyrrole ring. Ring-closure may be either at sulphur or nitrogen. In the synthetic approaches to thiazoles[15] it is well known that reaction of a halocarbonyl compound (XLIII) with an N-substituted thioamide (XLIV) affords an N-substituted thiazolium salt (XLV) and it was hoped to utilise 2-mercaptopyrroles (XLVI) which can be regarded as the tautomeric forms of thioamides in this reaction to form pyrrolo[2,1-b]thiazolium salts (XLVII) and by deprotonation pyrrolo[2,1-b]thiazoles (XLVIII).

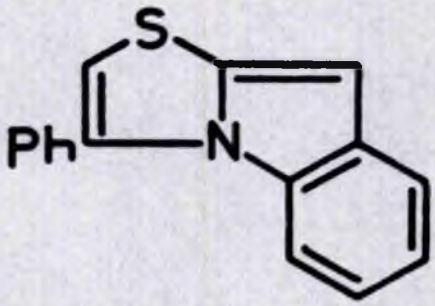
2-Mercaptopyrroles are unknown save 2-mercaptoindole (thioxindole) (XLIX) which is formed from oxindole and phosphorus pentasulphide in xylene. The literature method[16] for the reaction was found to be unsatisfactory and a modification was developed utilising an inert solid diluent to prevent inclusion of the product in the solid cake of reactants formed during reaction. The product was reacted with bromoacetone and phenacyl bromide in



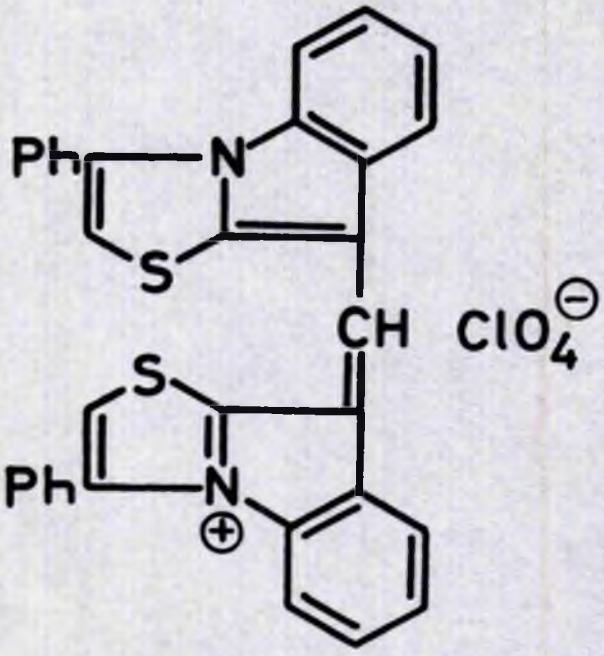
XLIX



L



LI

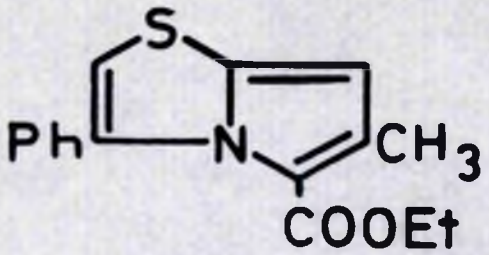


LII

the hope of forming the pyrrolo[2,1-b]thiazoles (L) and (LI) respectively. In the first case no useful product as detected with Ehrlichs reagent was formed while in the latter the amount formed was so small that it was only possible to isolate and characterise it as the dyestuff (LII) formed by treatment of the product with ethyl orthoformate and perchloric acid. The yield of the dyestuff from thioxindole was 0.15%.

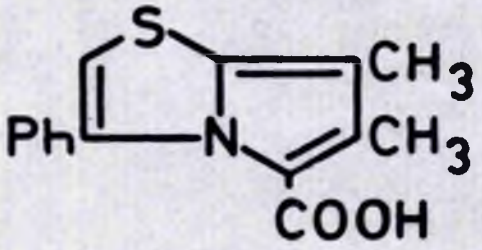
An attempt was then made to apply the reaction to simpler systems, the method chosen for the introduction of the mercapto group into a pyrrole being based on thiocyanation[17] followed by reduction. Considerable doubt exists[18,19] regarding the position of thiocyanation of pyrrole itself and for our work we chose a tri-substituted compound, ethyl 3,4-dimethylpyrrole-2-carboxylate. This was readily thiocyanated at the vacant 5-position using cupric thiocyanate in methanol. Attempted reduction of this compound using zinc and acetic acid afforded a mixture of products which by virtue of its high melting range and low solubility appears to contain mainly the corresponding dipyrryl disulphide formed by aereal oxidation of the mercaptan. Attempted reaction of this product and also of the reduction product, without isolation, with phenacyl bromide afforded a mixture containing unchanged halo-ketone which did not give a positive test with Ehrlichs reagent after hydrolysis with strong acid to effect removal of the ester group (LIII) - (LIV) - (LV).

The reasons for the lack of success of this method are unknown and in view of the poor results and the fail-



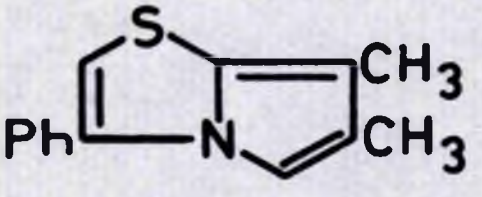
LIII

$H^{\oplus}$



LIV

$H^{\oplus}$



LV

ure of other workers[18] to obtain mercaptopyrrole from thiocyanopyrrole the approach was abandoned.

BIII. Properties of pyrrolo [2,1-b] thiazoles.

a) General.

The alkyl pyrrolo [2,1-b] thiazoles are either low melting solids or li uids with a pronounced naphthalene like odour. They rapidly decomposed under the influence of air and light to brightly coloured tars, a process accelerated by an increase in the number of alkyl substituents, especially when present in the pyrrole ring. Due to this instability they could not be analysed directly but instead were converted into stable solid derivatives with trinitrobenzene, picric acid and perchloric acid for analysis. The aryl pyrrolo [2,1-b] thiazoles with the exception of 3,6-dimethyl-7-phenyl-pyrrolo [2,1-b] thiazole which was a liquid were stable high-melting solids which were analysed directly.

b) Ultra-violet spectra of pyrrolo [2,1-b] thiazoles.

The ultra-violet spectra of the pyrrolo [2,1-b] thiazoles were recorded using solutions in cyclohexane. The results are shown in table I. The spectra consist essentially of two broad bands, a shoulder being displayed on that at lower wavelength in some cases and are typical aromatic spectra. There appears to be little correlation between the position and nature of substituent groups and the wavelengths of the extinction maxima save that groups attached to the 5- or 7-positions appear to be most significant in this context.

TABLE I

The ultra-violet absorption maxima (mμ) of pyrrolo[2,1-b] thiazoles in cyclohexane.

Compound	λmax.	log ε	λmax.	log ε	λmax.	log ε
Pyrrolo[2,1-b]thiazole	S218	3.9632	232	3.8915	282	3.7129
6-Methyl-pyrrolo[2,1-b]thiazole	224	4.1032			282	3.5955
2,6-Dimethyl-pyrrolo[2,1-b]thiazole	224	3.9887	S240	3.8641	280	3.5428
3,6-Dimethyl-pyrrolo[2,1-b]thiazole	225	4.0888	S251	3.5433	281	3.6998
5,6-Dimethyl-pyrrolo[2,1-b]thiazole	225	4.1325	S260	3.5354	294	3.4722
6,7-Dimethyl-pyrrolo[2,1-b]thiazole	213	4.1048	246	3.9402	288	3.5308
3,6,7-Trimethyl-pyrrolo[2,1-b]thiazole	214	4.1418			288	3.6892
5,6,7-Trimethyl-pyrrolo[2,1-b]thiazole	219	4.1176	S250	3.7644	299	3.4597
6-Methyl-2,3-tetramethylene-pyrrolo[2,1-b]thiazole	221	4.0592			279	3.8247
6-Phenyl-pyrrolo[2,1-b]thiazole	S244	3.8805	250	3.8972	265	3.9272
2-Methyl-6-phenyl-pyrrolo[2,1-b]thiazole	210	4.2598	S252	4.2452	268	4.3083
3-Methyl-6-phenyl-pyrrolo[2,1-b]thiazole	210	4.3253			263	4.3434
2,3-Tetramethylene-6-phenyl-pyrrolo[2,1-b]thiazole	S213	4.3139			265	4.3713

S denotes shoulder

c) Nuclear magnetic resonance spectra of pyrrolo[2,1-b] thiazoles.

The nuclear magnetic resonance spectra of 6-methyl-, 5,6-dimethyl-, 6,7-dimethyl- and 5,6,7-trimethylpyrrolo [2,1-b] thiazole were recorded using 10% solutions of the bases in carbon tetrachloride. The results are shown in table II, the assignations are based on the effect of replacement of a hydrogen atom by a methyl group and all the spectral features are readily accomodated. The range of chemical shifts of the ring protons is that in which heteroaromatic proton signals usually occur indicating the essentially aromatic nature of the system.

TABLE II. Chemical shifts (δ) in the proton magnetic resonance spectra of pyrrolo[2,1-b]thiazoles in carbon tetrachloride. (J values are in c./sec.).

	Ring Protons				Substituents			
	2-H	3-H	5-H	7-H	3-Me	5-Me	6-Me	7-Me
6-Methyl-pyrrolo[2,1-b] thiazole	6.32D J(2H-3H) 4.5	7.03D	6.78	5.9	—	—	2.2	—
5,6-Dimethyl-pyrrolo[2,1-b] thiazole	6.4D J(2H-3H) 4.1	7.05D	—	5.87	—	2.10 or 2.15	2.15 or 2.1	—
6,7-Dimethyl-pyrrolo[2,1-b] thiazole	6.32D J(2H-3H) 4.0	7.05D	6.78	—	—	—	2.10 or 2.05	2.05 or 2.10
3,6,7-Trimethyl-pyrrolo[2,1-b] thiazole	5.86 J(2H-3Me) 1.2	—	6.62	—	2.11D J(3Me-2H) 1.2	—	2.10 or 2.05	2.05 or 2.10

D denotes doublet; Q, quadruplet.

d) Trinitrobenzene complexes of alkyl pyrrolo[2,1-b] thiazoles.

All the alkyl pyrrolo[2,1-b]thiazoles readily formed stable charge-transfer complexes with trinitrobenzene in ethanol. The degree of charge transfer as judged from the colour of the products both in the solid state and in solution increases with the number of alkyl groups in the molecule, those in the pyrrole ring exerting a greater influence in this respect.

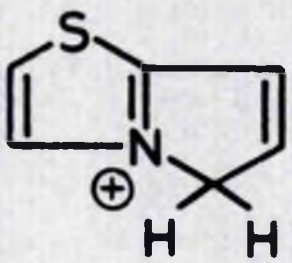
e) Pyrrolo[2,1-b]thiazolium salts.

1) Picrates

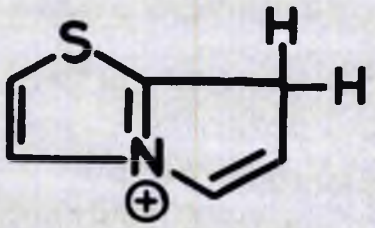
Picrates were formed from 6-methyl-, 5,6-dimethyl-, and 5,6,7-trimethylpyrrolo[2,1-b]thiazole. All of these were stable crystalline compounds and appeared to be salts rather than charge-transfer complexes even in the case of the 5,6,7-trimethyl compound. This assignation is based on the colour of the picrates both in the solid state and in solution and on the melting point behaviour which is without a transition of any type.

2) Perchlorates.

Perchlorates of pyrrolo[2,1-b]thiazoles were formed by the action of 70% perchloric acid on ethanolic solutions of the bases. In the case of certain 6-phenyl derivatives which are less basic, and hence the perchlorates are less stable, the preparation was carried out using acetonitrile as solvent. The parent base afforded a perchlorate which was too soluble in ethanol to allow isolation and methanol was used as solvent for this preparation. 5,6-Dimethylpyrrolo[2,1-b]thiazole



LVI



LVII

alone did not afford a crystalline perchlorate. The nicely crystalline perchlorates were obtained in yields in excess of 88% and more often in the cases of the alkyl compounds in yields exceeding 95%. The perchlorates of the alkyl compounds were readily purified by re-crystallisation and were used to characterise the unstable bases.

f) Ultra-violet spectra of pyrrolo[2,1-b]thiazolium salts.

The ultra-violet spectra of these salts were measured on solutions of the bases in methanol containing 1% (v/v) of 72% perchloric acid and the results are shown in table III. The spectra consist essentially of two broad bands, in some cases a shoulder is displayed on that at lower wavelength. Owing to the broadness of the latter band, together with the high solvent absorption in the region of absorption the wavelengths of the maxima may not be accurate and it is simpler to consider substituent effects on the long wavelength band. Introduction of a methyl group at the 6-position produces a bathochromic shift of 9 mμ, at the 2- or 3-position a shift of 7mμ in the same direction, in the 7-position a similar shift of 4 mμ but introduction of a methyl group in the 5-position causes very little or no change in the spectrum. This would suggest that the 5-position is not part of the conjugated system of the cation, that is to say the salt possesses structure (LVI) resulting from protonation at position 5- rather than structure (LVII) by protonation at position 7-. Little else of interest emerges from these spectra.

TABLE III

The ultra-violet absorption maxima (mμ) of pyrrolo[2,1-b]thiazoles in methanol containing 1% (v/v) of 72% perchloric acid.

Compound	max.	log	max.	log	max.	log
Pyrrolo[2,1-b]thiazole	208	3.6914			283	3.9396
6-Methyl-pyrrolo[2,1-b]thiazole	216	3.6442			292	4.0468
2,6-Dimethyl-pyrrolo[2,1-b]thiazole	224	3.7195			299	4.0511
3,6-Dimethyl-pyrrolo[2,1-b]thiazole	224	3.6728			299	4.0378
5,6-Dimethyl-pyrrolo[2,1-b]thiazole	215	3.7249			292	4.0319
6,7-Dimethyl-pyrrolo[2,1-b]thiazole	213	3.6511	227(S)	3.5763	297	4.0823
3,6,7-Trimethyl-pyrrolo[2,1-b]thiazole	225	3.5353			301	4.0511
5,6,7-Trimethyl-pyrrolo[2,1-b]thiazole	211	3.7299	225(S)	3.6047	296	4.0719
2,3-Tetramethylene-6-methyl-pyrrolo[2,1-b]thiazole	226	3.6894			310	4.0483
6-Phenyl-pyrrolo[2,1-b]thiazole	225	3.965			340	4.3790
2-Methyl-6-phenyl-pyrrolo[2,1-b]thiazole	227	4.1086			347	4.3728
3-Methyl-6-phenyl-pyrrolo[2,1-b]thiazole	225	3.9375			342	4.3807
2,3-Tetramethylene-6-phenyl-pyrrolo[2,1-b]thiazole	230	3.9362			353	4.3916
2,3-Benzo-6-phenyl-pyrrolo[2,1-b]thiazole	255	4.2898	272(S)	4.3118	361	3.9400
3,6-Dimethyl-7-phenyl-pyrrolo[2,1-b]thiazole	244	3.9109			307	3.9834

(S) denotes shoulder

g) Nuclear magnetic resonance spectra of pyrrolo[2,1-b]-thiazolium salts.

The nuclear magnetic resonance spectra of the following pyrrolo[2,1-b]thiazoles were measured in trifluoroacetic acid solutions: a) pyrrolo[2,1-b]thiazole, b) 6-methyl-, c) 2,6-dimethyl-, d) 3,6-dimethyl-, e) 5,6-dimethyl-, f) 6,7-dimethyl-, g) 3,6,7-trimethyl-, h) 5,6,7-trimethyl-, k) 2,3-tetramethylene-6-methyl-, l) 6-phenyl-, m) 2-methyl-6-phenyl-, n) 3-methyl-6-phenyl-, o) 2,3-tetramethylene-6-phenyl-, p) 2,3-benzo-6-phenyl-, and q) 3,6-dimethyl-7-phenylpyrrolo[2,1-b]thiazole. The compounds a) - d), f) - k) and q) were examined using solutions of the perchlorates in trifluoroacetic acid and the others using solutions of the bases in the same solvent, the spectrum of a solution of 2,3 dimethylthiazolium perchlorate r) in trifluoroacetic acid was also measured for purposes of comparison. The main aim of this study was a determination of the preferred position of protonation as has been achieved in the indolizine series.[20]

None of the spectra show a broad band or triplet which would arise from a proton bonded to nitrogen. The site of protonation must therefore be a carbon atom, a methylene or substituted methylene group being formed. The location of this site was determined by studying the effects of substitution in the molecule on the occurrence of signals and their multiplicity due to spin-spin coupling. We compare first the spectra of a) pyrrolo[2,1-b]thiazolium b) 6-methylpyrrolo[2,1-b]thiazolium f) 6,7-dimethylpyrrolo[2,1-b]thiazolium and h) 5,6,7-trimethylpyrrolo[2,1-b]thiazolium which are shown in

FIG. 1

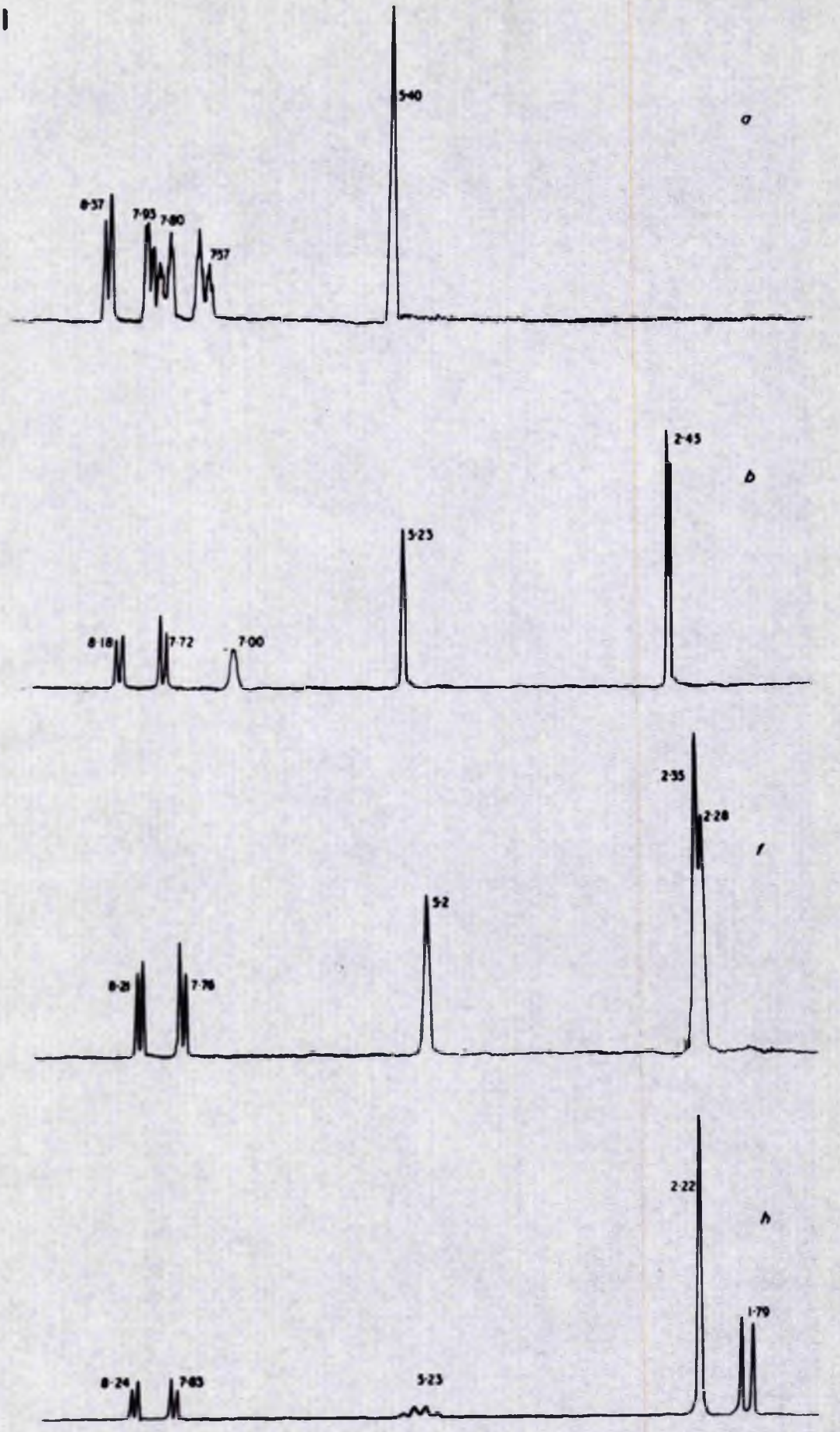

8·57
7·93
7·80
7·57
5·40
a
8·18
7·72
7·00
5·23
2·45
b
8·28
7·78
5·2
2·35
2·28
f
8·24
7·83
5·23
2·22
1·79
h

figure I. Substitution in the pyrrolo ring by methyl groups in most cases increases the shielding of the aromatic protons by a small amount (0 - 0.4p.p.m.). The spectrum of the parent salt shows three features: 1) a single peak at δ5.40. This is assigned to a methylene group on the basis of its spectral position. 2) Two doublets with equally spaced components at δ7.93 and δ8.37 (J 4c./sec.) arising from an AB system of two protons, 3) A further two doublets at δ7.37 and δ7.80 (J. 6c./sec.) due to another AB system. Integration of the spectrum shows unequivocally that the single peak and the AB quadruplets are each equivalent to two protons. There is some smaller splitting (1 - 2c/sec.) of these lines which will be dealt with later. Two features of the spectrum of the salt a) are also found in the spectra of b) 6-methyl- and f) 6,7-dimethylpyrrolo[2,1-b]thiazole: 1) The spectra of b) and f) show single peaks at δ5.23 and δ5.20, respectively, corresponding to the signal at δ5.40 assigned to a methylene group in pyrrolo[2,1-b]thiazolium. 2) They also show the low field AB pattern of pyrrolo[2,1-b]thiazolium with slightly increased shielding (0.1 - 0.2 p.p.m.). The integrals of the spectra confirm that each of these features corresponds to two protons as in the parent cation. The spectrum of h) 5,6,7-trimethylpyrrolo[2,1-b] shows one feature common to the spectra of a), b) and f), namely the low field AB system of two protons. The pattern of the low field quadruplet is thus unaltered by the progressive introduction of methyl groups at positions 6,7 and 5. A small diamagnetic displacement only is observed. Hence for all four salts this pattern

must arise from the protons of the thiazole ring, those at positions 2 and 3. These salts must consequently have resulted from protonation of the corresponding pyrrolo[2,1-b]thiazoles in the pyrrole ring. In the case of 6,7-dimethylpyrrolo[2,1-b]thiazole a methylene group can develop by protonation only at position 5. Furthermore the signals from the methylene protons of a) and b) occur in the same narrow spectral regions (δ5.20 - δ5.40) as that from the methylene protons of 6,7-dimethylpyrrolo[2,1-b]thiazolium and we can conclude that a) and b) are also produced by protonation at position 5. The signal of a methylene group resulting from protonation at position 7, would be expected to be substantially upfield relative to that resulting from protonation at position 5 since the latter is directly attached to the positive nitrogen atom. Indeed the 7-methylene signal of 7-H-5,6-dimethylpyrrolo[2,1-b]thiazolium occurs at δ4.13 (see below). The chemical shifts of the methylene protons of a), b) and f) are in agreement with the direct linking of the methylene group to a positively charged nitrogen atom and the progressive upfield shift of the methylene signal is as expected for the introduction of electron releasing methyl groups.

The interpretation of the residual features of the spectra of a), b) and f) agrees with the above conclusions. The upfield AB quadruplet of a) arises from H-6 and H-7. Although individual assignments cannot be made with certainty the high field components are tentatively assigned to H-7 on the basis of comparisons with the H-7 signals of other salts (see table IV). Each component of the multiplet is split into three lines

by spin-spin coupling to the methylene group, and the 6-H component appears to be equivalently couples to the proton at position 2 of the thiazole ring thus causing the formation of a quadruplet. The single peak in the spectrum of b) at δ 7.00 is assigned to the 7-proton and is weakly split (1.6c./sec.) by coupling to the 6-methyl group through four bonds.

In the spectrum of h) 5,6,7-trimethylpyrrolo[2,1-b] thiazolium an evenly spaced quadruplet at δ 5.23 occurs in place of the methylene singlets of a), b) and f) and is shown by integration to be equivalent to one proton. This is due to coupling of this proton with a methyl group attached to the same carbon atom, as is confirmed by the presence of a doublet at δ 1.79 equivalent to three protons and showing the same splitting (J 7.2c./sec.). This is independent evidence that protonation of 5,6,7-trimethylpyrrolo[2,1-b] thiazole occurs in the pyrrole ring and strengthens the conclusion that protonation in the pyrrole ring takes place in all four salts a), b),f) and h). The quartet occurs in the same spectral region as the methylene signals of a), b) and f) indicating that 5,6,7-trimethylpyrrolo[2,1-b] thiazole is also protonated at position 5. The 6- and 7-methyl protons of h) have identical chemical shifts giving a single line at δ 2.22 and the doublet at δ 1.79 is due to the 5-methyl group.

In the low field AB quadruplet from the thiazole ring protons we would expect the 3-proton signal to appear at lower field than that of the 2-proton and this is confirmed by examination of the spectra of 2,6- and 3,6-dimethylpyrrolo[2,1-b] thiazolium, c) and d) respec-

tively. The methyl group signals of the 6,7-dimethyl compound remain to be considered. The line at lower field has been assigned to the 6-methyl group as this would be expected to suffer greater deshielding due to its proximity to the positive nitrogen atom.

On the basis of the assignments for these four compounds the spectral assignments for the rest of the salts have been made as shown in table IV, these are in agreement with 5-protonation in all cases. It has been found possible to identify the 6-methyl proton signal in compounds having the 7-position unsubstituted by the small spin-spin coupling with the 7-proton, and similarly for the 2- and 3-methyl groups. In the phenyl compounds some portions of the spectra were obscured by the proton signals of the benzene ring and complete analysis was not possible in these cases. The two 2,3-tetramethylene compounds k) and o) displayed a pair of overlapping triplets each due to an α-methylene group spin-spin coupled to the adjacent β-methylene group. That at higher field is assigned to the 2-methylene group by analogy with protons in these positions. The β-methylene protons display a fairly broad band due to the multiplicity of spin-spin coupling present.

The spectrum of 5,6-dimethylpyrrolo[2,1-b] thiazolium 1) is unusual in that it displays evidence of two species resulting from 5- and 7-protonation respectively. Integration of the spectrum demonstrates that about 15% of the latter is present. This results in the spectrum of the former partially obscuring that of the latter in the regions of the aromatic and methyl protons and it has not

been possible to extract the complete spectrum of the 7-H species. The preponderance of the 5-H form is a reflection of the energetic favourability of 5-protonation even when sterically hindered and explains the wide melting range of the picrate of this compound.

The spectrum of pyrrolo[2,1-b]thiazolium perchlorate was also examined in deuterotrifluroacetic acid solution. No proton exchange was detected after several hours standing at room temperature. This behaviour is similar to that of indolizine, it is indicative of the high basicity of pyrrolo[2,1-b]thiazole and demonstrates that pyrrolo[2,1-b]thiazolium perchlorate and probably the other perchlorates used in this work are protonated at the 5-position in the solid state.

The 2- and 3-proton chemical shifts of all the compounds examined are similar to those of the corresponding protons in 2,3-dimethylthiazolium perchlorate r) indicating that in the pyrrolo[2,1-b]thiazolium salts the thiazole ring carries the bulk of the positive charge.

TABLE IV. Chemical shifts (δ) in the proton magnetic resonance spectra of Pyrrolo[2,1-b]thiazolium cations in trifluoroacetic acid. (J values are in c./sec.)

	Ring Protons					Substituents							
	2-H	3-H	5-H	6-H	7-H	2-CH_3	3-CH_3	5-CH_3	6-CH_3	7-CH_3	2-CH_2	3-CH_2	β-CH_2
(a) Pyrrolo[2,1-b] thiazole	7.93DD J(2H-3H) 4.0 J(2H-6H) 1.4	8.37D	5.40 J(5CH_2-6H) 1.4 J(5CH_2-7H) 1.7	7.90DQ J(6H-7H) 6.0 J(6H-5CH_2) 1.4 J(6H-2H) 1.4	7.37DT J(7H-5CH_2) 1.7								
(b) 6-Methyl-pyrrolo[2,1-b] thiazole	7.72D J(2H-3H) 4.0	8.18D	5.23		7.00Q J(7H-6CH_3) 1.6				2.45D J(6CH_3-7H) 1.6				
(c) 2,6-Dimethyl-pyrrolo[2,1-b] thiazole		7.88Q J(3H-2CH_3) 1.25	5.15		6.89Q J(7H-6CH_3) 1.6	2.63D J(2CH_3-3H) 1.25			2.41D J(6CH_3-7H) 1.6				
(d) 3,6-Dimethyl-pyrrolo[2,1-b] thiazole	7.33Q J(2H-3CH_3) 1.3		5.03		6.96Q J(7H-6CH_3) 1.6		2.58D J(3CH_3-2H) 1.3		2.45D J(6CH_3-7H) 1.6				
(e) 5,6-Dimethyl-pyrrolo[2,1-b] thiazole													
5-H form	7.82D J(2H-3H) 4.0	8.20D	5.24Q J(5H-5CH_3) 7.0		6.99Q J(7H-6CH_3) 1.6			1.81D J(5CH_3-5H) 7.0	2.40D J(6CH_3-7H) 1.6				
7-H form					4.13								
(f) 6,7-Dimethyl-pyrrolo[2,1-b] thiazole	7.76D J(2H-3H) 3.9	8.21D	5.20						2.35	2.28			
(g) 3,6,7-Trimethyl-pyrrolo[2,1-b] thiazole	7.33		4.99				2.59		2.35	2.24			

TABLE IV (Contd)

	Ring Protons					Substituents							
	2-H	3-H	5-H	6-H	7-H	2-CH_3	3-CH_3	5-CH_3	6-CH_3	7-CH_3	2-CH_2	3-CH_2	βCH_2
(h) 5,6,7-Trimethyl-pyrrolo[2,1-b] thiazole	7.85D J(2H-3H) 4.1	8.24D	5.23Q J(5H-5CH_3) 7.2					1.79D J(5CH_3-5H) 7.2	2.22	2.22			
(k) 6-Methyl-2,3-tetramethylene-pyrrolo[2,1-b] thiazole			4.98		6.94Q J(7H-6CH_3) 1.5				2.45D J(6CH_3-7H) 1.5		2.02T	2.12T	2.86B J(αCH_2-βCH_2) 3.0
(l) 6-Phenyl-pyrrolo[2,1-b] thiazole	7.77D J(2H-3H) 4.0	8.25D	5.55										
(m) 2-Methyl-6-phenyl-pyrrolo[2,1-b] thiazole		7.91Q J(3H-2CH_3) 1.8	5.63		7.58	2.67D J(2CH_3-3H) 1.8							
(n) 3-Methyl-6-phenyl pyrrolo[2,1-b] thiazole			5.56		7.69		2.64D J(3CH_3-2H) 1.2						
(o) 6-Phenyl-2,3-tetramethylene-pyrrolo[2,1-b] thiazole			5.47		7.47						2.05T	2.15T	2.95B J(αCH_2-βCH_2) 3.0
(p) 2,3-Benzo-6-phenyl-pyrrolo[2,1-b] thiazole			5.88										
(q) 3,6-Dimethyl-7-phenylpyrrolo[2,1-b] thiazole	7.37		5.2				2.67D J(3CH_3-2H) 1.3		2.51				
(r) 4,5-Dimethyl-thiazolium	7.86D J(2H-3H) 4.0	8.02D			(4-CH_3 4.19	5-CH_3 3.02)							

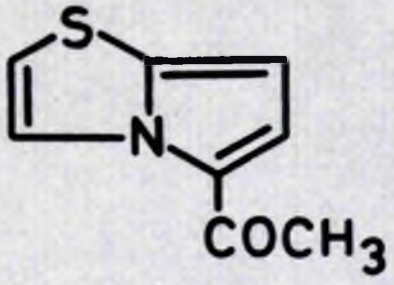
For multiplets D = doublet, T = triplet, Q = quadruplet, B = broad peak.

BIV. Substitution reactions of pyrrolo[2,1-b]thiazoles.

In the whole of this work great use was made of thin layer chromatography (T.L.C.) for the rapid qualitative analysis of substitution products. The method could differentiate mono- and disubstituted compounds and also positional isomers and served in all cases as a criterion of purity.

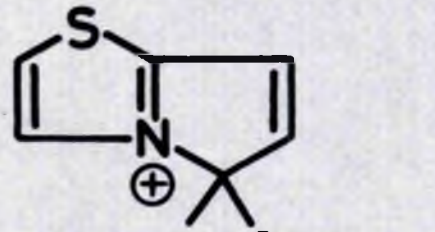
a) Examination of the acetylated products from the Chichibabin cyclisation.

As a preliminary to an examination of the direct substitution problem an investigation was made of the nature of the acetyl compounds produced in the sodium acetate - acetic anhydride cyclisation of the quaternary salts from thiazoles and α-haloketones. This, it was hoped would serve as a preliminary examination of electrophilic substitution reactions and would afford some evidence of the yield in the cyclisation and hydrolysis stages. The first product examined was that from 3-acetonyl-2-methyl thiazolium bromide. Analysis by T.L.C. showed the presence of two components of quite different polarities which were readily separated by chromatography on alumina affording mono- and diacetyl-6-methylpyrrolo[2,1-b]thiazoles in yields totalling 90% from the quaternary salt. The overall yield of 6-methylpyrrolo[2,1-b]thiazole from quaternary salt is 65% indicating a hydrolysis yield of 73%, the losses presumably being due to dyestuff formation as discussed in section BIIb. The crude products from 3-(3-butan-2-onyl)-2-methylthiazolium bromide, 3-acetonyl-2-ethylthiazolium bromide and 3-acetonyl-2-ethyl-4-methylthiazolium bromide were analysed by T.L.C. and in each case found to contain one

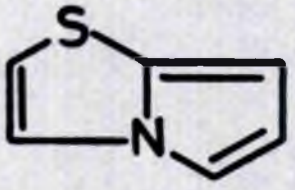


LVIII

$H^{\oplus}$



LIX



$+CH_3CO^{\oplus}$

LX

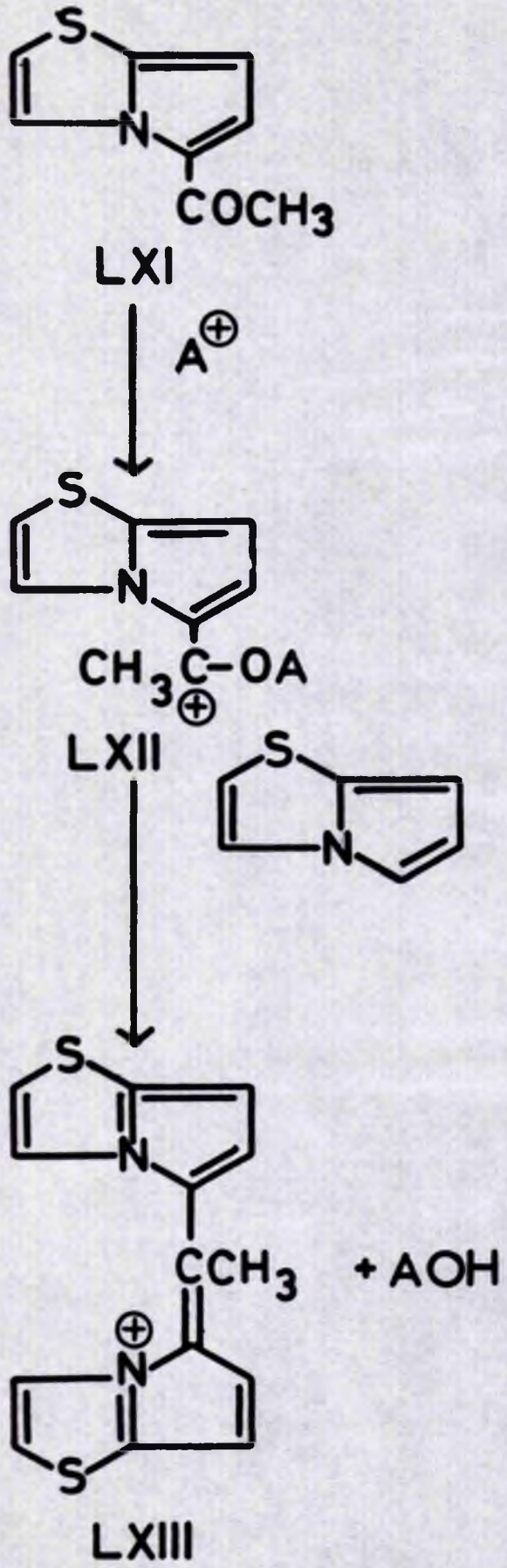
component only. Sublimation of the crude products followed in some cases by recrystallisation resulted in the isolation of the monoacetylated 5,6-dimethyl-, 6,7-dimethyl- and 5,6,7-trimethylpyrrolo[2,1-b]thiazoles respectively. The yields were 46%, 90% and 97% respectively from the corresponding quaternary salts. These should be compared with the respective yields 30%, 89% and 98% of the corresponding bases from the quaternary salts. The quantitative hydrolysis yields in the last two cases are as would be expected for such highly alkylated compounds since the electron releasing methyl groups increase the electron density on the peripheral carbon atom carrying the acetyl group, facilitating proton addition leading to deacetylation (LVIII) - (LX). The poorer yield in the case ofthe first compound may be a result of the greater complexity of the working up procedure utilised in the preparation of the base.

Substitution reactions on 6-methylpyrrolo[2,1-b]thiazole.

At the outset of this work it was hoped that the substitution reactions of the system would be examined using the parent base. However as a result of the poor yield in the synthesis of this compound insufficient was available for study and the work on the substitution chemistry of pyrrolo[2,1-b]thiazole has been carried out on the next most simple compound available, the 6-methyl-derivative. In the ensuing discussion it will be assumed for clarity that monosubstitution takes place at position 5 of the pyrrolo[2,1-b]thiazole nucleus, that this is indeed so will be established at a later point,

b) Acetylation.

Reaction of 6-methylpyrrolo[2,1-b]thiazole with boiling acetic anhydride either with or without the addition of sodium acetate afforded almost quantitative yields of a monoacetyl compound identical to that isolated from the cyclisation product. Reaction with acetic anhydride alone at an elevated temperature, under pressure in a sealed tube afforded the same mono- and diacetyl compounds as from the cyclisation. However the molar ratio of diacetyl to monoacetyl was 3:4 as opposed to 5:2 in the cyclisation product. This is presumably due to a higher acidity in the cyclisation reaction due to the presence of hydrobromic acid. In view of this some attempts were made to effect a catalysed di-acetylation of 6-methylpyrrolo[2,1-b]thiazole in acetic anhydride. In the first reaction one equivalent of perchloric acid was used as catalyst by


S
N
COCH3
LXI
A⊕
S
N
CH3C–OA
⊕
LXII
S
N
S
N
CCH3
+AOH
⊕N
S
LXIII

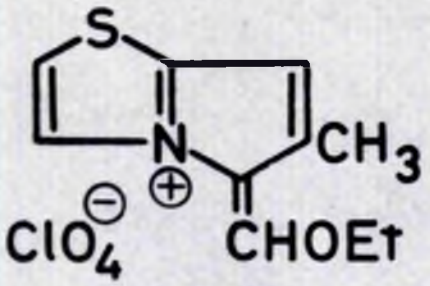
carrying out the reaction on 6-methylpyrrolo[2,1-b] thiazolium perchlorate. Extensive decomposition took place with the formation of an intensely violet solution which after working up afforded a product containing only traces of acetylated pyrrolo[2,1-b] thiazoles together with a large quantity of more polar materials. An attempt was then made to utilise stannic chloride as a catalyst, in acetic anhydride at room temperature. The product contained mainly unchanged base, traces of mono- and diacetyl-6-methylpyrrolo[2,1-b] thiazoles and some more polar material. Using the same catalyst in boiling acetic anhydride the product contained a number of compounds all more polar than diacetyl-6-methylpyrrolo-[2,1-b] thiazole. The results of these experiments may be due to the added acid in each case acting as a catalyst for the condensation of acetyl compound either with itself or with unchanged base (LXI) - (LXIII) a process which can possibly lead to polymeric products. Alternatively in the stannic chloride case the metal ions may in some way cause desulphurisation and the pyrrole compounds produced polymerise or otherwise decompose under the influence of acid.

c) Nitration.

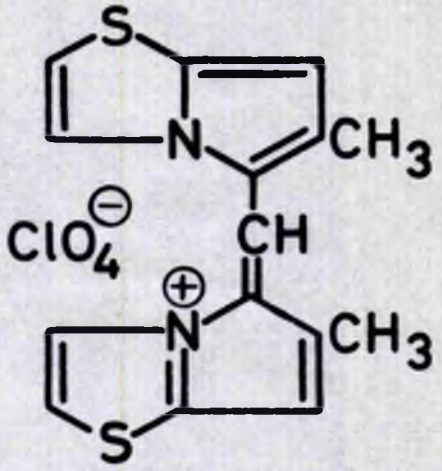
In our first attempts to nitrate 6-methylpyrrolo [2,1-b] thiazole the reagent adopted was cupric nitrate in acetic anhydride. This has been used successfully in the azulene[21] series. Using a variety of reaction times only small quantities of product were isolated which were shown by T.L.C. to be mixtures of very polar materials. This may be due to oxidative degradation

of the base or the copper ions present may cause some form of reaction at sulphur leading to decomposition. Reaction was then attempted using tetranitromethane which has also been successfully applied in the azulene series.[22] A product was isolated from this reaction which was neither mono- or dinitro-6-methylpyrrolo [2,1-b] thiazole and whose structure will be discussed later.

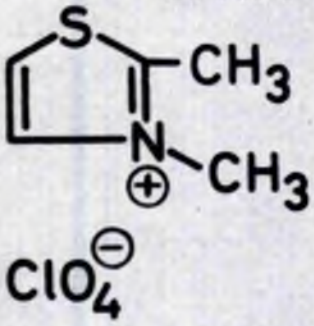
Attempts were then made to effect the mononitration of the monoacetyl-6-methylpyrrolo [2,1-b] thiazole in the hope that the product would be of use in structural assignations in a similar method to that employed in the indolizine series (see section AIIIb 4). Reaction with cupric nitrate in acetic anhydride again resulted in extensive decomposition no nitroacetyl compound being detected in the product by T.L.C. The use of a short reaction time afforded a product containing decomposition products together with unchanged starting material. Obviously in this case nitration is too slow a reaction to compete with the decomposition processes. The use of tetranitromethane afforded a product containing mainly unreacted starting material even when prolonged reaction times were employed. T.L.C. analysis of the products showed the presence of two compounds whose polarity and yellow colour indicated that they might be the desired nitroacetyl-6-methylpyrrolo [2,1-b] thiazole and possibly some mononitro-6-methylpyrrolo [2,1-b] thiazole resulting from electrophilic displacement of acetyl by nitro. However the quantities present were so minute as to render isolation impossible.



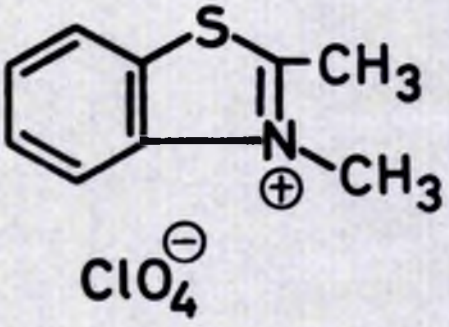
LXIV



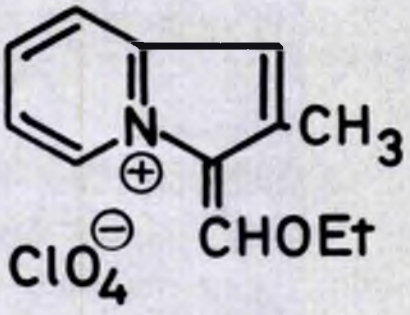
LXV



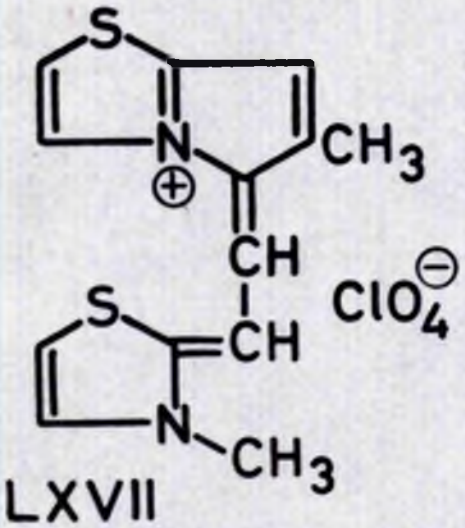
LXVI



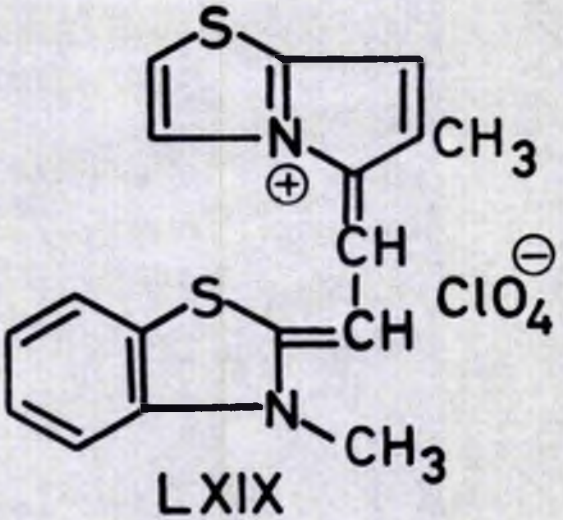
LXVIII



LXX



LXVII

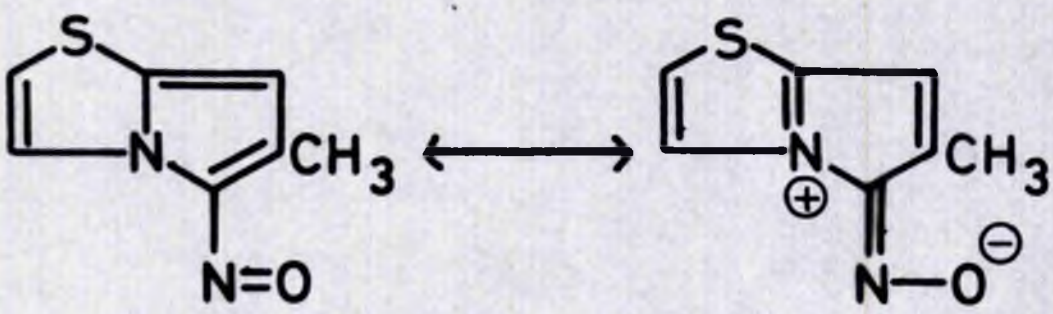


LXIX

d) Formylation.

Reaction of 6-methylpyrrolo[2,1-b]thiazole with dimethylformamide and phosphorus oxychloride at -35° afforded monoformyl-6-methylpyrrolo[2,1-b]thiazole in good yield. The aldehyde is extremely light sensitive and all operations with it had to be carried out in the dark. An attempt was made to obtain the same aldehyde via the ethoxymethylene-6-methylpyrrolo[2,1-b]thiazolium salt in an analogous manner to that utilised in the indolizine series (see section A III b3). Reaction of 6-methylpyrrolo[2,1-b]thiazolium perchlorate with a large excess of ethyl orthoformate in ethanol afforded a mixture of the required ethoxymethylene-6-methylpyrrolo[2,1-b]thiazole (LXIV) together with a red dyestuff which is presumably the monomethine salt (LXV). The presence of the former is shown by the formation of an orange dimethine cyanine dyestuff (LXVII) on treatment of the mixture with 2,3-dimethylthiazolium perchlorate (LXVI) and piperidine.

Using acetonitrile as solvent preliminary formation of the yellow ethoxymethylene salt occurred followed by decomposition to the red dyestuff. The employment of short reaction times permitted the isolation of the former which rapidly became red in air presumably due to decomposition to a dyestuff and the material was characterised by condensation with 2,3-dimethylbenzothiazolium perchlorate (LXVIII) to afford the dimethine cyanine dyestuff (LXIX). This behaviour is in contrast to that of the analogous 2-methylindolizine which readily affords the fairly stable 3-ethoxymethylene salt (LXX). This



LXXI LXXII

difference must be due to a greater positive charge density on the methylene carbon atom of the pyrrolo [2,1-b] thiazole derivative (LXIV), and hence an enhanced electrophilic activity causing a greater extent of dyestuff-forming intermolecular reaction. That is to say the thiazole ring is not capable of accomodating a positive charge as readily as the pyridine ring. An attempt was made to isolate the monomethine dyestuff (LXV) by reaction of 6-methylpyrrolo[2,1-b] thiazolium perchlorate with a small excess of ethyl orthoformate in ethanol. The product was inhomogeneous and could not be purified by recrystallisation due to the presence of polymeric material.

e) Nitrosation.

Reaction of 6-methylpyrrolo[2,1-b] thiazole in dilute hydrochloric acid with one and a half equivalents of sodium nitrite afforded an almost quantitative yield of mononitroso-6-methylpyrrolo[2,1-b] thiazole (LXVI). This compound was extremely soluble in water and could not be satisfactorily extracted from aqueous alkaline solution using ether. This is presumably due to a high degree of polarisation in the ground state (LXVII) as is the case with the nitrosoindolizines (see section A III d3).

In view of the failure of attempts to effect direct nitration of 6-methylpyrrolo[2,1-b] thiazole attempts were made to oxidise the nitroso group in nitroso-6-methyl-pyrrolo[2,1-b] thiazole to nitro for comparison with the nitration product. The reagent used was hydrogen peroxide in aqueous and acetic acid solutions. A wide variety of reaction times and temperatures were employed but T.L.C. analysis of the product in each case showed

only traces of what appeared to be nitro-6-methylpyrrolo[2,1-b]thiazole together with varying quantities of starting material, and some more polar material presumably resulting from oxidative disruption of the ring system.

f) Trifluoroacetylation.

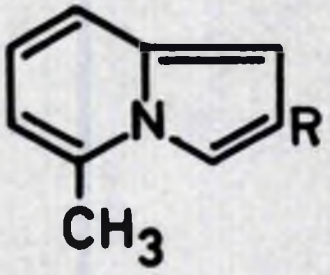
Treatment of 6-methylpyrrolo[2,1-b]thiazole with trifluoroacetic anhydride in methylene chloride afforded a high yield of a homogeneous monotrifluoroacetyl-6-methylpyrrolo[2,1-b]thiazole. The product which rapidly decomposed in air, was hydrolised by alkali to the corresponding 6-methylpyrrolo[2,1-b]thiazole carboxylic acid. This substance, as would be expected in view of the high electron density at the peripheral carbon carrying the carboxylic acid group, rapidly decarboxylates at its melting point.

g) Tropylation.

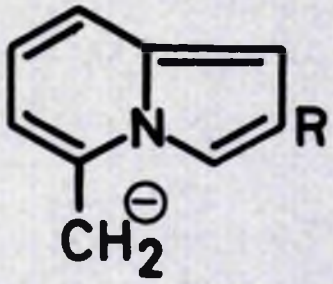
The remaining substitution reaction of 6-methylpyrrolo[2,1-b]thiazole studied was tropylation by reaction with tropylium perchlorate. This reaction, involving a preformed carbonium ion salt is one of the simplest examples of electrophilic substitution that can be envisaged. Reaction of 6-methylpyrrolo[2,1-b]thiazole with one equivalent of tropylium perchlorate in acetonitrile afforded a non-crystalline product which was shown by T.L.C. analysis to contain two compounds, presumably the mono- and ditropyl-6-methylpyrrolo[2,1-b]thiazoles, the amount of the latter being about 2%. The product decomposed within thirty minutes under the influence of air and light into a green tar and could

not be converted into a crystalline molecular complex with trinitrobenzene or trinitrofluorenone.

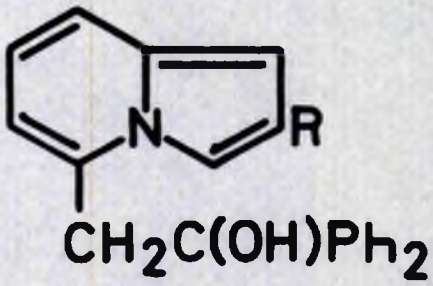
Reaction of the base with two equivalents of tropylium perchlorate afforded a homogeneous product which was shown be T.L.C. analysis to be identical to the minor component from the first reaction, i.e. the di-tropylated compound. This material was non-crystalline and unstable and did not afford a solid derivative with trinitrobenzene or trinitrofluorenone. The general instability of these products is in agreement with our previous observations on the alkylated pyrrolo[2,1-b] thiazoles and the inability to form complexes is presumably due to steric factors, the bulky tropyl side groups preventing the close approach of the acceptor molecule necessary for charge transfer complex formation to take place.



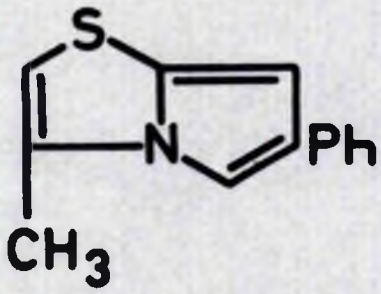
LXXIII



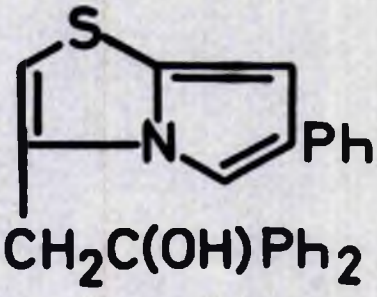
LXXIV



LXXV



LXXVI

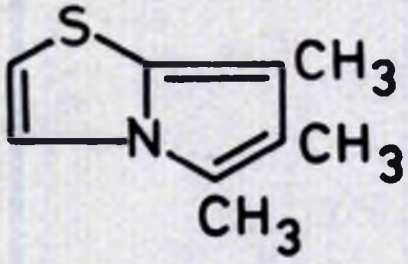


LXXVII

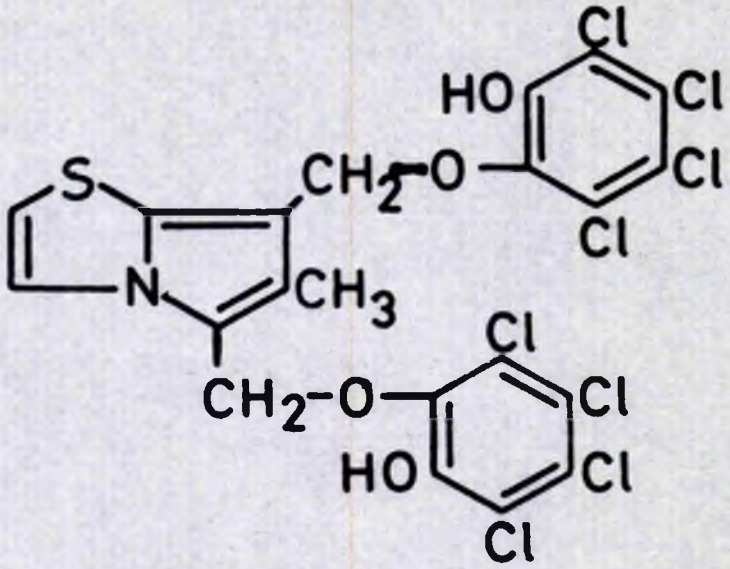
IV. Reactions of methyl groups in pyrrolo[2,1-b]thiazoles.

An examination was made of the properties of methyl groups attached to the pyrrolo[2,1-b]thiazole nucleus. In the analogous indolizine system Boekelheide[23] has shown that the 5-methyl groups in 5-methyl- and 5-methyl-2-phenylindolizine are acidic, readily losing a proton on treatment with butyl lithium (LXXIII) - (LXXIV) (R=H or Ph). The resulting anion (LXXIV)(R=H or Ph) reacts in the normal manner, for example with benzophenone affording the carbinol (LXXV) (R=H or Ph). In the pyrrolo[2,1-b]thiazole series we chose to examine the 3-methyl-6-phenyl compound (LXXVI) as the electron attracting phenyl group should render it more reactive towards nucleophiles than the 3,6-dimethyl- or 3-methyl- compound. Reaction of this compound with butyl lithium under conditions identical to those employed by Boekelheide for 5-methyl-2-phenylindolizine followed by reaction with benzophenone afforded none of the appropriate carbinol (LXXVII). This would suggest a lower degree of ground state polarisation in pyrrolo[2,1-b]thiazole than in indolizine resulting in a higher electron density in the thiazole ring than in the pyridine ring and hence a reduced electrophilic character of groups attached to the ring.

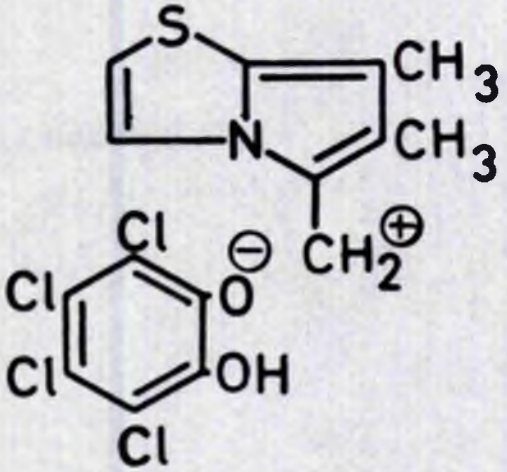
Fraser[5] has shown that methyl groups at the 1- and 3-positions in indolizine readily suffer hydride abstraction by quinones or triphenylmethyl perchlorate. Reaction of 1,2,3-trimethylindolizine with one equivalent of tetrachloro-o-benzoquinone for instance affords a quantitative yield of the corresponding quinol. In the reaction of the analogous 5,6,7-trimethylpyrrolo[2,1-b]thiazole



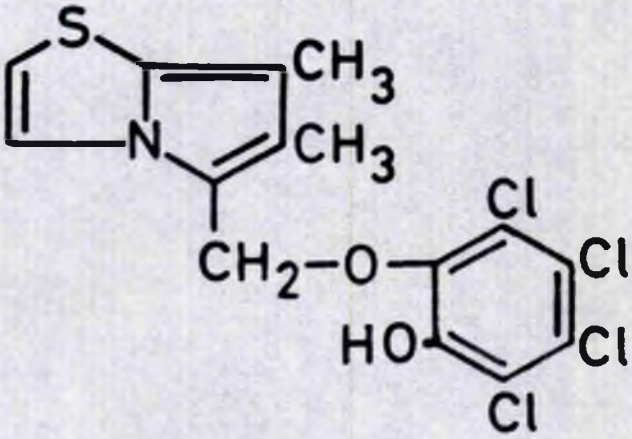
LXXVIII



LXXIX



LXXX



LXXXI

(LXXVIII) with tetrachloro-o-benzoquinone we observed the instantaneous formation at room temperature of the ether, 5,7-bis-(2,3,4,5 tetrachloro-6-hydroxyphenoxymethyl)-6-methylpyrrolo[2,1-b]thiazole (LXXIX). This substance is cleaved by acid to tetrachlorocatechol and decomposes on heating in solution or in the solid state to violet dyestuff-like materials.

The difference between the behaviour of 5,6,7-trimethylpyrrolo[2,1-b]thiazole and 1,2,3-trimethyl indolizine is presumably due to a higher positive charge density on the methylene carbon of the intermediate (LXXX) resulting from removal of one hydride ion, this causes formation of the ether (LXXXI) and further dehydrogenation to the diether (LXXII). This greater charge density is due to a lesser degree of accomodation of the positive charge on the thiazole ring than on the pyridine ring of indolizine and is in agreement with our findings in the reaction of 6-methylpyrrolo[2,1-b]thiazolium perchlorate with ethyl orthoformate and in the reaction of 3-methyl-6-phenyl-pyrrolo[2,1-b]thiazole with butyl lithium.

TABLE V. Chemical shifts (δ) in the proton magnetic resonance spectra of substituted 6-methylpyrrolo[2,1-b]thiazoles in deutero-chloroform. (J values are in c./sec.)

	2-H	3-H	5-H	7-H	6-Me	
Monoacetyl-6-methyl-pyrrolo[2,1-b]thiazole	6.78D	8.73D	—	6.18	2.48 or 2.51	Acetyl-Me 2.51 or 2.48
	J(2-H-3-H) 4.5					
Mononitroso-6-methyl-pyrrolo[2,1-b]thiazole	7.02D	8.87D	—	6.53	2.85	
	J(2-H-3-H) 4.5					
Monoformyl-6-methyl-pyrrolo[2,1-b]thiazole	6.77D	8.45D	—	6.05	2.43	Formyl-H 9.58
	J(2-H-3-H) 4.5					
Diacetyl-6-methyl-pyrrolo[2,1-b]thiazole	7.03D	8.86D	—	—	2.83	Acetyl-Me's 2.57 and 2.58
	J(2-H-3-H) 4.5					
5,6-Dimethyl-pyrrolo[2,1-b]thiazole	6.4D	7.05D	—	5.87	2.15 or 2.1	
	J(2-H-3-H) 4.1					
6,7-Dimethyl-pyrrolo[2,1-b]thiazole	6.32D	7.05D	6.78		2.10 or 2.05	
	J(2-H-3-H) 4.0					

D denotes doublet.

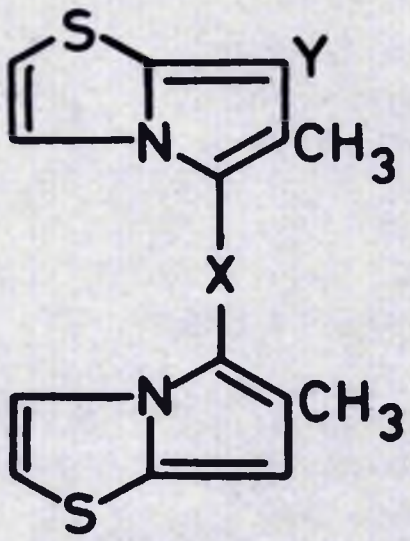
B VI. Nuclear magnetic resonance spectra and structures of substituted 6-methylpyrrolo[2,1-b]thiazoles.

The nuclear magnetic resonance spectra of mono-, and diacetyl-, monoformyl-, and mononitroso-6-methylpyrrolo[2,1-b]thiazoles were recorded using 10% solutions of the compounds in deuterochloroform, save in the case of the diacetyl compound, which is only slightly soluble in this solvent, a saturated solution being used. The spectra are summarised in table V, the spectra of 5,6- and 6,7-dimethylpyrrolo[2,1-b]thiazole being included for comparison. Although the last two spectra were recorded using solutions in carbon tetrachloride the results are comparable as this change of solvents is known to effect chemical shifts and coupling constants by only very small amounts.

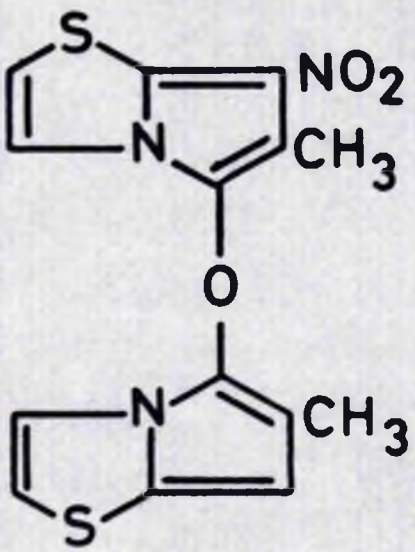
All of the spectra of the monosubstituted 6-methylpyrrolo[2,1-b]thiazoles show an AB quadruplet in the aromatic region due to the 2,3 proton system of the thiazole ring. The only other peak in this region, a singlet due to the residual pyrrole ring proton is always upfield of the AB system and the general pattern of the spectrum is similar to that of 5,6-dimethylpyrrolo[2,1-b]thiazole indicating that 5-substitution has occurred. Furthermore the position of the signal of the residual pyrrole ring proton (δ6.05 - δ6.2) is always upfield of the position of the 5-proton signal of the alkyl pyrrolo[2,1-b]thiazoles (δ6.6 - δ6.8) (see table II) but is only slightly downfield (0.2p.p.m.) of the 7-proton signal of the bases. This is as expected for the presence of electron attracting groups and confirms that 5-substitution has occurred. The spectrum of diacetyl-6-methylpyrrolo[2,1-b]thiazole

shows only the two proton AB quadruplet in the aromatic region indicating that it is 5,7-disubstituted. These results indicate that in electrophilic substitution as in the case of protonation the 5-position is the preferred site of attack, followed by the 7-position. Hence the monoacetylated 3,6,7- and 5,6-dimethyl, and 3,6,7-trimethylpyrrolo[2,1-b]thiazoles must be substituted at the 5-,7-, and 5-positions respectively. In the case of 6-methylpyrrolo[2,1-b]thiazolemonocarboxylic acid derived from the unstable monotrifluoroacetyl-6-methylpyrrolo[2,1-b]thiazole the compound was not sufficiently soluble to allow an N.M.R. spectrum to be recorded but it is reasonable to assume that this compound also is 5-substituted.

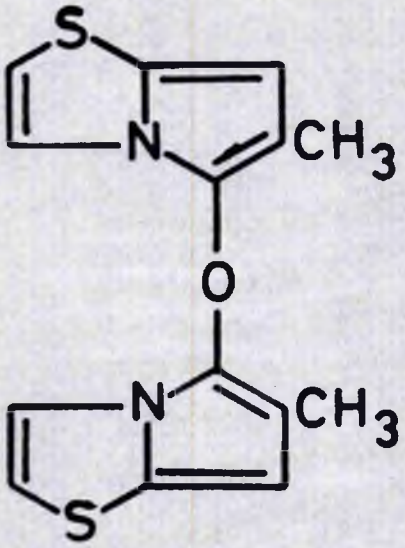
The spectrum of the product from the attempted nitration of 6-methylpyrrolo[2,1-b]thiazole was also obtained using a 10% solution of the compound in deuterochloroform. The spectrum is entirely different from the spectra of the substitution products and contains the following features: a) an AB quadruplet the components of which have δ7.23 and δ7.03 (J=4.4c./sec.), b) a second AB quadruplet the components having δ7.03 and δ6.65 (J=4.4c./sec.), c) a single line at δ6.24,d) a single line at δ2.40, and e) a single line at δ2.13. The upfield doublet of the low field AB system is superimposed on the downfield doublet of the second AB system affording a pattern of three doublets in an intensity ratio of 1:2:1. The ratio of intensities for the whole spectrum is 1:2:1:1:3:3 and on the basis of this and the positions of the signals the following assignments may be made: a) and b) two AB systems of aromatic protons due to the 2,3 proton



LXXXII



LXXXIII



LXXXIV

systems of two different pyrrolo[2,1-b]thiazole nuclei, c) a single proton at the 7-position of a pyrrolo[2,1-b] thiazole nucleus, this assignation is based on the position of the signal with respect to the AB systems (see above) and, d) and e) two 6-methyl groups in two different pyrrolo [2,1-b]thiazole nuclei. Thus one can write (LXXXII) as a structure for the compound. The empirical formula of the product $C_{14}H_{11}N_3O_3S_2$ would then suggest (LXXXIII) as the structure of this compound. The AB system signals and methyl group signal at lower field arise from the nucleus carrying the nitro substituent as a result of the electron attracting nature of this group.

The formation of this compound 7-nitro-6,6-dimethyl-5,5-di(pyrrolo[2,1-b]thiazolyl) ether in a tetranitromethane nitration is surprising and without precedent, presumably some form of free radical oxidation produces the ether (LXXXIV) which is then nitrated to give (LXXXIII).

PART C

Introductory Notes.

Melting points were determined on a Kofler-type heating stage.

Ultra-violet and visible spectra were recorded on a "Unicam" S.P.700 instrument.

Infra-red spectra were recorded with a Grubb-Parsons Type G.S.2A. instrument.

Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer operating at 60 megacycles per sec., at a sweep rate of 1 cycle per sec. per sec. The intensities of the signals were measured by the built-in integrator. Tetramethylsilane was used as the internal reference. Chemical shifts are given on the δ scale, the absolute values being accurate to $\pm$ 0.015 p.p.m. on the precalibrated 500c./sec. scale. J values were measured on the 100 c./sec. scale and are accurate to $\pm$0.1 c./sec.

Micro-analyses were performed by Drs. Weiler and Strauss, Oxford.

Samples for analysis were dried for 12 hours in vacuo over phosphorus pentoxide and potassium hydroxide.

Perchloric acid refers to the 70-72% (w/w), analar grade.

Chromatography was on activated alumina, Spence Type H, 100/200 mesh and on Woelm alkali free, activity grade I alumina the latter being denoted neutral alumina.

Thin layer chromatography was on 250mμ layers of silica gel prepared using the commercial Desaga spreader.

Unless otherwise stated the compounds were spotted as solutions in chloroform, eluted with ether and the chromatogram developed by exposure to iodine vapour.

Gas liquid chromatography was on a Pye "Argon"

instrument using a 10% Apiezon L on Celite column at 150° unless otherwise stated.

C.I Preparation of thiazoles.

2-Bromothiazole was prepared by the method of Ganapathi and Venkataraman.[24]

2-Methylthiazole was prepared by the method of Hantzsch.[25]

2-Ethylthiazole.

A mixture of dry propionamide (146 g., 2.0 mole.) and phosphorus pentasulphide (88g., 0.4mole.) in dry benzene (120 ml.) was heated, with stirring, under reflux, on a boiling water bath until a black oily lower layer formed (ca. 2hr.). Meanwhile a solution of bromoacetaldehyde was prepared by heating bromoacetal (295g., 1.5mole.) and anhydrous oxalic acid (135g., 1.5mole.) under reflux, at 160° for 5 hr. The latter solution, after cooling to room temperature, was added to the mixture at such a rate that the benzene refluxed gently. After the completion of the addition the mixture was heated at 100° for 1 hr., a mixture of concentrated hydrochloric acid (120ml.) and water (60 ml.) added, and heating continued for a further 1 hr. The mixture was steam distilled to remove benzene, basified with 50% sodium hydroxide solution and steam distilled. The distillate was extracted with ether, the ether solution dried (K_2CO_3), the solvent evaporated and the residue distilled affording 2-ethylthiazole (36 g., 21%), b.p. 144-6°.

Lit.[26] b.p. 73-6°/70 mm.

2,4-Dimethylthiazole was prepared by the method of Kurkjy and Brown.[2]

2,5-Dimethylthiazole was prepared by the method of Kurkjy and Brown.[2]

2-Ethyl-4-methylthiazole.

A mixture of dry propionamide (146 g., 2 mole.) and phosphorus pentasulphide (88 g., 0.4 mole.) in dry benzene (120 ml.) was heated, with stirring, under reflux, on a boiling water bath until a black oily lower layer formed (ca. 2 hr.). Bromoacetone (137 g., 1 mole.) was added dropwise at such a rate that the benzene gently refluxed. After the addition was complete the mixture was heated for 1 hr., a solution of concentrated hydrochloric acid (10 ml.) in water (50 ml.) added and heating continued for a further 1 hr. The mixture was steam distilled to remove benzene, made alkaline with 50% sodium hydroxide solution and steam distilled. The distillate was extracted with ether, the ether extract dried (K_2CO_3), the solvent evaporated, and the residue distilled affording 2-ethyl-4-methylthiazole (79.5 g., 62.5%), b.p. 162-3°.
Lit.[27] b.p. 162°.

2-Methyl-4-phenylthiazole.

A mixture of dry acetamide (59.5 g., 1 mole.) and phosphorus pentasulphide (44 g., 1.2 mole.) in dry benzene (60 ml.) was heated, with stirring, under reflux, on a boiling water bath until a black oily lower layer formed (ca. 1.5 hr.). A solution of phenacyl bromide (99.5 g., 1.5 mole.) in benzene (100 ml.) was added dropwise at such a rate that the benzene refluxed gently. After the addition was complete the mixture was heated for 1 hr., a solution of concentrated hydrochloric acid (5 ml.) in water (25 ml.) added and heating continued for a further 1 hr. The mixture was steam distilled to remove benzene,

made alkaline with 50% sodium hydroxide solution and steam distilled. The distillate was extracted with ether, the ether extract dried (K_2CO_3), the ether distilled off and the residue distilled at reduced pressure affording 2-methyl-4-phenylthiazole (138 g., 79%),

b.p. 140-142°/10 mm.

Lit.[28] b.p. 284°.

2-Benzyl-4-methylthiazole.

Phenylacetamide (40 g., 0.3 mole.) and phosphorus pentasulphide (13.4 g., 0.06 mole.) in dry benzene (200 ml) were heated, with stirring, under reflux, on a boiling water bath for 1 hr. Bromoacetone (20.6 g., 0.15 mole.) was added dropwise over 30 min. and the mixture heated for 2 hr. A solution of concentrated hydrochloric acid (2 ml.) in water (20 ml.) was added and heating continued for a further 1 hr. Water (200 ml.), was added and the mixture steam distilled to remove benzene, made alkaline with 50% sodium hydroxide solution and steam distilled. The distillate was extracted with ether, the ether solution dried (K_2CO_3), and the solvent evaporated. Distillation of the residue at reduced pressure afforded 2-benzyl-4-methylthiazole (16 g., 56%), b.p. 95-7°/0.1 mm.

Lit.[29] b.p. 150° /14 mm.

2-Methyl-4,5-tetramethylenethiazole.

A mixture of dry acetamide (150 g., 2.5 mole.) and phosphorus pentasulphide (111 g., 0.5 mole.) in dry benzene (150 ml.) was heated, with stirring, under reflux, on a boiling water bath until a black oily lower layer formed (ca. 2 hr.). 2-Chlorocyclohexanone (166 g., 1.25 mole.) was then added dropwise at such a rate as to main-

tain gentle refluxing. After completion of the addition the mixture was heated for 1 hr., a solution of concentrated hydrochloric acid (10 ml.) in water (50 ml.) added and heating continued for a further 1 hr. The mixture was steam distilled to remove benzene, basified with 50% sodium hydroxide solution and steam distilled. The distillate was extracted with ether, the ether solution dried (K_2CO_3) and the solvent evaporated. Distillation of the residue at reduced pressure afforded 2-methyl-4,5-tetramethylenethiazole (93 g., 49%), b.p. 97-9°/7 mm.
Lit.[30] b.p. 110° /12 mm.

2-Methylbenzothiazole was prepared by the method of Hofmann.[31]

C.II Synthesis of pyrrolo[2,1-b]thiazoles

a) Attempted Scholtz synthesis of pyrrolo[2,1-b]thiazole.

A solution of 2-methylthiazole (5 g., 0.05 mole.) in acetic anhydride (25 ml.) was heated at 200° in a sealed tube for 5 hr. The tube and contents were cooled in solid carbon dioxide before opening and the contents poured into cold water (200 ml.). The solid material adhering to the tube was extracted with boiling acetone (2x25 ml.) which was added to the aqueous mixture. After standing for 12 hr. at room temperature water (800 ml.) was added and the mixture thoroughly extracted with chloroform. The chloroform extract was washed with 0.5N sulphuric acid, water, potassium carbonate solution, again with water and dried (Na_2SO_4). After evaporation of the chloroform the residue was dissolved in methylene chloride (25 ml.) and the solution filtered through a column of alumina (8cm. x 2.5 cm.) using ether (800 ml.) for elution. Evaporation of the ether afforded a brown tarry paste (150 mgm.) which was examined by thin layer chromatography. This showed the presence of at least six components, two of which had similar R_f values to mono- and diacetyl-6-methylpyrrolo[2,1-b]thiazoles.

b) Synthesis of pyrrolo[2,1-b]thiazoles by the Chichibabin reaction.

6-Methylpyrrolo[2,1-b]thiazole.

A solution of 2-methylthiazole (9.9 g., 0.1 mole.) and bromoacetone (13.7 g., 0.1 mole.) in dry chloroform (10 ml.) was allowed to stand at room temperature for 72 hr. A pale yellow oil which separated from the mixture crystallised on being scratched. The pale yellow crystalline 3-acetonyl-2-methylthiazolium bromide (21 g., 89%) was filtered off, washed well with ether and air dried. It decomposes >200°.

The bromide could not be recrystallised satisfactorily and a sample was converted into the perchlorate for analysis by the action of a 10% excess of perchloric acid on a cold 5% solution of the bromide in ethanol. 3-Acetonyl-2-methylthiazolium perchlorate (92%) crystallised on cooling and recrystallised from ethanol as colourless needles, m.p. 124-6°.

Found: N,5.48

$C_7H_{10}ClNO_5S$ requires N,5.62%.

A mixture of the bromide (11.8 g., 0.05 mole.) and fused sodium acetate (8.2 g., 0.1 mole.) in acetic anhydride (120 ml.) was refluxed for 2 hr., then poured into water (700 ml.). The product was allowed to stand at room temperature for 12 hr. and extracted with methylene chloride. The extract was washed with water, dilute potassium carbonate solution, again with water, and dried (Na_2SO_4). Evaporation of the solvent afforded the crude acetylated pyrrolo[2,1-b]thiazole as a dark red oil which

slowly solidified.

The crude cyclisation product (3.67 g.) was refluxed for 3 hr. with a mixture of concentrated hydrochloric acid (18 ml.) and water (60 ml.). The solution was made alkaline by the addition of solid sodium hydroxide and steam distilled. The distillate was extracted with ether, and the ether extract was dried (K_2CO_3) and evaporated. The residual yellow oil distilled at 10 mm. (block temp. 90-95°) affording 6-methylpyrrolo[2,1-b] thiazole (1.5 g., 65.7% from the salt) as colourless needles, m.p. 57-8°, which rapidly became violet and then black in air.

6-Phenylpyrrolo[2,1-b]thiazole.

A solution of 2-methylthiazole (9.9g., 0.1 mole.) and phenacyl bromide (19.9 g., 0.1 mole.) in dry ethanol (100 ml.) was refluxed for 12 hr. The mixture was cooled, ether (100 ml.) was added and the 2-methyl-3-phenacyl-thiazolium bromide (26.5 g., 89%) was filtered off, washed well with ether, and recrystallised from ethanol, affording colourless cubes, m.p. 204-5.5°.

Found: Br, 26.4.

$C_{12}H_{12}BrNOS$ requires Br, 26.8%.

A mixture of the bromide (14.9 g., 0.05 mole.) and fused sodium acetate (8.2 g., 0.1 mole.) in acetic anhydride (150 ml.) was refluxed for 4 hr. The cooled mixture was poured into water (1 l.), allowed to stand at room temperature for 12 hr. and extracted with chloroform. The chloroform extract was washed with water, dilute potassium carbonate solution, again with water and dried (Na_2SO_4). Evaporation of the solvent afforded the crude

acetylated pyrrolo[2,1-b]thiazole (9.3 g.) as a viscous yellow oil.

The cyclisation product (9.3 g.) was refluxed with concentrated hydrochloric acid (80 ml.) for 3 hr. The resulting dark violet solution was diluted with water (1.5 l.) and extracted four times with ether. The combined ether extracts were washed with water, sodium carbonate solution, again with water, dried (K_2CO_3), and the ether was evaporated. The dark brown tarry residue was distilled at 0.1 mm. (block temp. 125-30°) and the colourless sublimate of 6-phenyl-pyrrolo[2,1-b]thiazole (1.94 g., 19.5% from the salt) crystallised from acetone as colourless needles, m.p. 200-202°.

Found: C,72.40;H,4.58;N,7.07;S,16.09.

$C_{12}H_9NS$ requires C,72.33;H,4.55;N,7.03;S,16.10%.

2,6-Dimethylpyrrolo[2,1-b]thiazole.

A solution of 2,5-dimethylthiazole (11.3 g., 0.1 mole.) and bromoacetone (13.7 g., 0.1 mole.) in dry chloroform (16 ml.) was refluxed for 4 hr. On cooling 3-acetonyl-2,5-dimethylthiazolium bromide (22.5 g., 90%) crystallised as yellow cubes which were filtered off, washed well with ether and dried in vacuo. It had m.p. 172-4°.

The bromide could not be recrystallised satisfactorily and a sample was converted into the perchlorate for analysis by the action of a 10% excess of perchloric acid on a cold 5% ethanolic solution of the bromide. 3-Acetonyl-2,5-dimethylthiazolium perchlorate (93%) crystallised from the cooled solution and was recrystallised from ethanol as colourless needles, m.p. 156.5-8.°

Found: N,5.10.

$C_8H_{12}ClNO_5S$ requires N,5.19%.

A mixture of the bromide (12.5 g., 0.05 mole.) and fused sodium acetate (8.2 g., 0.1 mole.) in acetic anhydride (125 ml.) was refluxed for 2 hr. The cooled mixture was added to water (1 l.). The resulting mixture was allowed to stand at room temperature for 12 hr. and then extracted with chloroform. The chloroform extract was washed with water, dilute potassium carbonate solution, again with water and dried (Na_2SO_4). Evaporation of the solvent afforded the crude acetylated pyrrolo [2,1-b] thiazole (10.5 g.) as a brown solid.

The crude cyclisation product (2.1 g.) was refluxed for 4 hr. with a mixture of concentrated hydrochloric acid (7 ml.) and water (30 ml.). The resulting solution was made alkaline by the addition of solid sodium hydroxide and steam distilled. The distillate was extracted with ether and the ether extract was dried (K_2CO_3) and evaporated. The residual yellow solid was distilled at 10 mm. (block temp. 105-110°) affording 2,6-dimethylpyrrolo[2,1-b] thiazole (0.99 g. 65% from the salt) as colourless plates, m.p. 80-81° (sublimes at >75°), which rapidly turned brown and then black in air.

3,6-Dimethylpyrrolo[2,1-b]thiazole.

A solution of 2,4-dimethylthiazole (22.6 g., 0.2 mole.) and bromoacetone (27.4 g., 0.2 mole.) in dry chloroform (20 ml.) was allowed to stand at room temperature for 60 hr. A dark red oil which separated from the solution crystallised on being scratched. Ether (50 ml.) was added and the solution allowed to stand for 2 hr. at room temperature. The pale yellow 3-acetonyl-2,4-di-

methylthiazolium bromide (40.6 g., 81%) was filtered off, washed well with ether and upon crystallisation from ethanol formed colourless cubes, m.p. 208-11° (with decomposition).

Found: N,5.60; S,12.69.

$C_8H_{12}BrNOS$ requires N,5.60; S,12.79%.

The bromide (12.5 g., 0.05 moles.), fused sodium acetate (8.2 g., 0.1 mole.), and acetic anhydride (120 ml.) were refluxed for 2 hr. The cooled mixture was added to water (1 l.). The resulting mixture was allowed to stand at room temperature for 12 hr. and extracted with chloroform. The chloroform extract was washed with water, dilute potassium carbonate solution, again with water, and dried (Na_2SO_4). Evaporation of the solvent afforded the crude acetylated pyrrolo[2,1-b]thiazole (10.7 g.) as a brown tarry solid.

The crude cyclisation product (3.6 g.) was refluxed for 3 hr. with a mixture of concentrated hydrochloric acid (20 ml.) and water (60 ml.). The solution was made alkaline by the addition of solid sodium hydroxide and steam distilled. The distillate was extracted with ether, the ether solution was dried (K_2CO_3) and the solvent was evaporated. The residual yellow oil, distilled at 10 mm. (block temp. 105-110°) afforded 3,6-dimethylpyrrolo[2,1-b]thiazole (1.56 g.62% from the salt) as a colourless oil which rapidly became brown and then black in air.

3,6-Dimethylpyrrolo[2,1-b]thiazole

A mixture of 2-methylthiazole (5.94 g., 0.06 mole.) and methyl α-bromoethyl ketone (9 g., 0.06 mole.) was

heated at 50° for 22 hr. Fused sodium acetate (9.84 g., 0.12 moles.) and acetic anhydride (150 ml.) were added and the mixture refluxed for 2 hr. The cooled mixture was poured into water (1 l.), allowed to stand at room temperature for 12 hr. and extracted with chloroform. The chloroform extract was washed with water, dilute potassium carbonate solution, again with water and dried (Na_2SO_4). Evaporation of the solvent afforded the crude acetylated pyrrolo[2,1-b]thiazole (10.93 g.) as a green oil which partially solidified to a tarry paste.

The crude cyclisation product (2.2g.) was refluxed for 2 hr. with a mixture of acetic acid (25 ml.), water (25 ml.), and concentrated hydrochloric acid (11 ml.). The solution was cooled, diluted with water (150 ml.), made alkaline by the addition of solid sodium hydroxide and steam distilled. The distillate was extracted with ether, the ether extract was washed with (2x200 ml.) portions of 0.5% sulphuric acid followed by water, and dried (K_2CO_3). The solvent was evaporated and the residual yellow oil distilled at 10 mm. (block temp. 110-15°) affording 5,6-dimethylpyrrolo[2,1-b]thiazole (0.54 g., 30% from methyl α-bromoethyl ketone and 2-methylthiazole.) as a pale yellow oil which darkened in air.

6,7-Dimethylpyrrolo[2,1-b]thiazole.

A solution of 2-ethylthiazole (5.65g., 0.05 mole.) and bromoacetone (6.85 g., 0.05 mole.) in dry chloroform (5 ml.) was refluxed for 6 hr. Acetone (30 ml.) was added to the cooled solution and the very hygroscopic colourless 3-acetonyl-2-ethylthiazolium bromide (8.02 g., 64%) filtered off, washed well with ether and dried in

vacuo. Owing to its extremely hygroscopic nature the m.p. could not be obtained.

A sample was converted to the perchlorate for analysis by the action of a 10% excess of perchloric acid on a 5% solution of the bromide in ethanol. 3-acetonyl-2-ethylthiazolium perchlorate (94%) crystallised on cooling and recrystallised from ethanol as colourless needles, m.p. 139-41°. Found: N,5.33.

$C_8H_{12}ClNO_5S$ requires N,5.19%.

A mixture of the bromide (5 g., 0.02 mole.) and fused sodium acetate (3.3 g., 0.04 mole.) in acetic anhydride (50 ml.) was refluxed for 2 hr., then poured into water (400 ml.). After 12 hr. at room temperature the mixture was extracted with chloroform. The chloroform extract was washed with water, dilute potassium carbonate solution, again with water, and dried (Na_2SO_4). Evaporation of the solvent afforded the crude acetylated pyrrolo[2,1-b]thiazole (3.83 g.) as a green crystalline solid.

The crude cyclisation product (1.28 g.) was refluxed for 2 hr. with a mixture of glacial acetic acid (10 ml.), water (10 ml.), and concentrated hydrochloric acid (5 ml.). The solution was cooled, diluted with water (150 ml.), made alkaline by the addition of solid sodium hydroxide and steam distilled. The distillate was extracted with ether, the ether extract was dried (K_2CO_3), and the solvent was evaporated. The residual yellow oil was distilled at 10 mm. (block temp. 105-10°) affording 6,7-dimethylpyrrolo[2,1-b]thiazole (0.89 g., 89% from the salt) as a colourless oil which very rapidly became blue and then black in air.

2-Methyl-6-phenylpyrrolo[2,1-b]thiazole.

A solution of 2,5-dimethylthiazole (22.6 g., 0.2 mole.) and phenacyl bromide (39.8 g., 0.2 mole,) in dry ethanol (120 ml.) was refluxed for 10 hr. 2,5-Dimethyl-3-phenacylthiazolium bromide (53 g., 85%) was filtered from the cooled solution, washed with a little ethanol and upon recrystallisation from ethanol formed colourless needles, m.p. 212-12.5° (darkens >205°).

Found: N, 4.25.

$C_{13}H_{14}BrNOS$ requires N, 4.49%.

The bromide (31.2 g., 0.1 mole), fused sodium acetate (16.4 g., 0.2 mole.), and acetic anhydride (310 ml.) were refluxed for 2 hr., then poured into water (2 l.), and the mixture allowed to stand at room temperature for 12 hr. before being extracted with chloroform. The chloroform extract was washed with water, dilute potassium carbonate solution, again with water, and dried (Na_2SO_4). Evaporation of the solvent afforded the crude acetylated pyrrolo[2,1-b]thiazole (26.7 g.) as a viscous brown oil which slowly solidified.

The crude cyclisation product (26.7 g.) was refluxed for 6 hr. with a mixture of dioxan (160 ml.), water (100 ml.), and concentrated hydrochloric acid (20 ml.). The mixture was diluted with water (2 l.) and extracted with chloroform. The chloroform extract was washed with water, dilute potassium carbonate solution, again with water, and dried (Na_2SO_4). Evaporation of the solvent afforded a green oil which was distilled at 0.1 mm. (block temp. 140-5°). The sublimate of 2-methyl-6-phenylpyrrolo[2,1-b]thiazole (7.65 g., 36% from the salt.) crystallised from ethanol as colourless plates, m.p. 200-3°

with decomposition (sublimes >150°).

Found: C,73.04; H,5.35; N,6.70; S,15.28.

$C_{13}H_{11}NS$ requires C,73.20; H,5.20; N,6.58; S,15.03%.

3-Methyl-6-phenylpyrrolo[2,1-b]thiazole was prepared by the method of Kondo and Nagasawa.[7]

3,6,7-Trimethylpyrrolo[2,1-b]thiazole.

A solution of 2-ethyl-4-methylthiazole (12.7 g., 0.1 mole.) and bromoacetone (13.7 g., 0.1 mole.) in chloroform (13 ml.) was refluxed for 12 hr. After it had cooled, ethyl acetate (3 vols.) was added and the brown amorphous 3-acetonyl-2-ethyl-4-methylthiazolium bromide (23.7 g., 86%) filtered off, washed well with ether and dried in vacuo, m.p. 142-5° (with decomposition.).

The bromide was hygroscopic and could not be recrystallised satisfactorily, neither could it be converted into a stable crystalline perchlorate. Accordingly the picrate was prepared for analysis by mixing saturated, boiling, ethanolic solutions of equimolecular quantities of the bromide and picric acid. 3-Acetonyl-2-ethyl-4-methylthiazolium picrate (88%) crystallised on cooling and recrystallisation from ethanol afforded yellow needles, m.p. 161-3° (softens >150°).

Found: N,13.65.

$C_{15}H_{16}N_4O_8S$ requires N,13.59%.

The bromide (13.2 g., 0.05 mole.), fused sodium acetate (8.2 g., 0.1 mole.) and acetic anhydride (140 ml.) were refluxed for 2 hr., then poured into water (1 l.). The mixture was allowed to stand at room temperature for 12 hours, then extracted with chloroform. The chloroform extract was washed with water, dilute potassium carbonate

solution, again with water, and dried (Na_2SO_4). Evaporation of the solvent afforded the crude acetylated pyrrolo[2,1-b]thiazole (10.4 g.) as a brown oil which slowly solidified.

The crude cyclisation product (1.04 g.) was refluxed for 2 hr. with a mixture of glacial acetic acid (10 ml.), and concentrated hydrochloric acid (5 ml.). The mixture was cooled, diluted with water (100 ml.), made alkaline by the addition of solid sodium hydroxide and steam distilled. The distillate was extracted with ether, the ether extract was dried (K_2CO_3) and evaporated. The residual yellow oil was distilled at 10 mm. (block temp. 115-20°) affording 3,6,7-trimethylpyrrolo[2,1-b]thiazole (0.81 g., 98% from the salt.) as colourless needles, m.p. 44-5°, which rapidly became green and then black in air.

5,6,7-Trimethylpyrrolo[2,1-b]thiazole.

A solution of 2-ethylthiazole (5.65 g., 0.05 mole.) and methyl α-bromoethyl ketone (7.55 g., 0.05 mole.) in dry chloroform (5 ml.) was refluxed for 7 hr. After cooling, ethyl acetate (50 ml.) was added and the extremely hygroscopic brown 3-(3-butan-2-onyl)-2-ethylthiazolium bromide (11.3 g., 86%) filtered off, washed well with ethyl acetate, and dried in vacuo. Owing to its extremely hygroscopic nature the m.p. could not be obtained.

A mixture of the bromide (5.28 g., 0.02 mole.) and fused sodium acetate (3.28 g., 0.04 mole.) in acetic anhydride was refluxed for 2 hr. The mixture was cooled, diluted with water (150 ml.), and made alkaline by the addition of solid sodium hydroxide. The mixture was steam distilled and the distillate extracted with ether. The

ether extract was dried (K_2CO_3) and the solvent evaporated. The residual yellow oil was distilled at 10 mm. (block temp. 130-5°) affording 5,6,7-trimethylpyrrolo[2,1-b]thiazole (1.99 g., 60% from the salt.) as a pale yellow oil.

6-Phenylbenzo[b]pyrrolo[2,1-b]thiazole.

A solution of 2-methylbenzothiazole (30 g., 0.2 mole.) and phenacyl bromide (39.8 g., 0.2 mole.) in dry chloroform (80 ml.) was refluxed for 6 hr. The mixture was cooled and the 2-methyl-3-phenacylbenzothiazolium bromide (15 g., 21.5%) filtered off and washed well with ether. The volume of the mother liquors and washings was reduced to 100 ml. by distillation and the resulting mixture refluxed for a further 15 hr. affording a further quantity (23 g., 32.8%) of salt (Total yield, 38 g., 54.3%). Crystallisation from methanol-acetone (1:1) afforded colourless prisms, m.p. 233.5-5.5°.

Lit.[4], m.p. 228-9°.

A mixture of the bromide (34.8 g., 0.1 mole.) and fused sodium acetate (16.4 g., 0.2 mole.) in acetic anhydride (350 ml.) was refluxed for 4 hr. The cooled mixture was poured into water (2 l.), and the product allowed to stand at room temperature for 12 hr. before being extracted with chloroform. The extract was washed with water, dilute potassium carbonate solution, again with water, and dried (Na_2SO_4). Evaporation of the solvent afforded the crude acetylated pyrrolo[2,1-b]thiazole (30 g.) as a brown oil.

The crude cyclisation product (3 g.) was refluxed for 3 hr. with a mixture of concentrated hydrochloric acid

(10 ml.) and glacial acetic acid (10 ml.). The resulting dark red solution was diluted with water (300 ml.) and extracted with ether. The ether extract was washed with water, potassium carbonate solution, again with water and dried (K_2CO_3). Evaporation of the ether and distillation of the residual dark brown oil at 0.1 mm. (block temp. 150-5°) afforded a pale yellow sublimate of 6-phenylbenzo[b]pyrrolo[2,1-b]thiazole (1.03 g., 41.4% from the salt.) which crystallised from ethanol as lustrous colourless needles, m.p. 124.5-5°.

Lit.[4] m.p. 127 -9°.

Found: C,77.16; H,4.47; N,5.54; S,12.60 .
$C_{16}H_{11}NS$ requires C,77.07; H,4.45; N,5.62; S,12.86%.

2,6-Dimethyl-7-phenylpyrrolo[2,1-b]thiazole.

A mixture of 2-benzyl-4-methylthiazole (9.45 g., 0.05 mole.) and bromoacetone (6.85 g., 0.05 mole.) was heated at 70° for 8 hr. The resulting brown gum was triturated with acetone affording yellow prisms of 3-Acetonyl-2-benzyl-4-methylthiazolium bromide (13.9 g., 85.4%) which were filtered off, washed well with ether and air dried, m.p. 165-8° (decomp.).

The bromide could not be recrystallised satisfactorily and a sample was converted to the perchlorate for analysis by the action of a 10% excess of perchloric acid on a cold 5% ethanolic solution of the bromide. 3-Acetonyl-2-benzyl-4-methylthiazolium perchlorate (95%) crystallised on cooling and recrystallised from ethanol as colourless plates, m.p. 159-61°.

Found: N,3.94.
$C_{14}H_{16}ClNO_5S$ requires N,4.05%.

The bromide (9.78 g., 0.03 mole), fused sodium acetate (4.92g., 0.06 mole.) and acetic anhydride (100 ml.) were refluxed for 2 hr. The cooled mixture was added to water (800 ml.). The resulting mixture was allowed to stand at room temperature for 12 hr. before being extracted with methylene chloride. The methylene chloride extract was washed with water, dilute potassium carbonate solution, again with water, and dried (Na_2SO_4). Evaporation of the solvent afforded the crude acetylated pyrrolo[2,1-b] thiazole (7.77 g.) as a black tarry paste.

The crude cyclisation product (7.77 g.) was refluxed for 5 hr. with a mixture of concentrated hydrochloric acid (40 ml.), glacial acetic acid (80 ml.), and water (80 ml.). The solution was diluted with water (2 l.) and extracted with chloroform. The chloroform solution was washed with water, sodium carbonate solution, again with water and dried (Na_2SO_4). Evaporation of the solvent and distillation of the residual red oil at 0.1 mm. (block temp. 140°) afforded 3,6-dimethyl-7-phenylpyrrolo[2,1-b]thiazole (0.435 g., 6.4% from the salt.) as a colourless oil.

6-Methyl-2,3-tetramethylenepyrrolo[2,1-b]thiazole.

A solution of 2-methyl-4,5-tetramethylenethiazole (15.3 g., 0.1 mole.) and bromoacetone (13.7 g., 0.1 mole.) in dry chloroform (15 ml.) was refluxed for 12 hr. After cooling, ethanol (30 ml.) was added followed by perchloric acid (10 ml., 0.125 mole.). Filtration of the cooled mixture afforded 3-acetonyl-2-methyl-4,5-tetramethylene-thiazolium perchlorate (16.2 g., 52%) which was washed well with ether and crystallised from ethanol as colourless prisms, m.p. 130-2°.

Found: N,4.35.

$C_{11}H_{16}ClNO_5S$ requires N,4.52%.

A mixture of the perchlorate (9.3 g., 0.03 mole) and fused sodium acetate (4.92 g., 0.06 mole) in acetic anhydride (100 ml.) was refluxed for 2 hr., poured into water (1 l.) and the mixture allowed to stand at room temperature for 12 hr. before being extracted with chloroform. The chloroform extract was washed with water, dilute potassium carbonate solution, again with water, and dried (Na_2SO_4). Evaporation of the solvent afforded the crude acetylated pyrrolo[2,1-b]thiazole (8.45 g.) as a red-brown oil.

The crude cyclisation product (8.45 g.) was refluxed for 4 hr. with a mixture of glacial acetic acid (85 ml.), water (85 ml.) and concentrated hydrochloric acid (43 ml.). The solution was cooled, diluted with water (200 ml.), made alkaline by the addition of solid sodium hydroxide and steam distilled. The distillate was extracted with ether, the ether solution was dried (K_2CO_3) and the solvent was evaporated. The residual yellow oil was distilled at 10 mm. (block temp. 160-5°) affording 6-methyl-2,3-tetramethylenepyrrolo[2,1-b]thiazole (4.3 g. 75% from the salt.) as colourless prisms, m.p. 55.5-6.5°, which rapidly became brown in air.

6-Phenyl-2,3-tetramethylenepyrrolo[2,1-b]thiazole.

A solution of 2-methyl-4,5-tetramethylenethiazole (15.3 g., 0.1 mole) and phenacyl bromide (19.9 g., 0.1 mole) in ethanol (50 ml.) was refluxed for 12 hr. After cooling and the addition of ether (100 ml.) 2-methyl-3-phenacyl-4,5-tetramethylenethiazolium bromide (28.2 g.,

82%) was filtered off, washed well with ether and recrystallised from acetonitrite as colourless prisms, m.p. 204-6° (with decomposition).

Found: N,3.85.

$C_{16}H_{18}BrNOS$ requires N,3.98%.

A mixture of the bromide (17.6 g., 0.05 mole) and fused sodium acetate (8.2 g., 0.1 mole.) in acetic anhydride (150 ml.) was refluxed for 2 hr., then poured into water (1 l.), and the mixture allowed to stand for 12 hr. at room temperature before being extracted with chloroform. The chloroform extract was washed with water, dilute potassium carbonate solution, again with water, and dried (Na_2SO_4). Evaporation of the chloroform afforded the crude acetylated pyrrolo[2,1-b]thiazole (12.03 g.) as a brown semicrystalline paste.

The cyclisation product (12.03 g.) was refluxed for 4 hr. with a mixture of glacial acetic acid (120 ml.), water (120 ml.), and concentrated hydrochloric acid (60 ml.). The mixture was cooled, diluted with water (2 l.) and extracted with chloroform. The chloroform extract was washed with water, dilute potassium carbonate solution, again with water, and dried (Na_2SO_4). Evaporation of the solvent and sublimation of the brown crystalline residue at 0.1 mm. (block temp. 165-70°) afforded a colourless sublimate of 6-phenyl-2,3-tetramethylenepyrrolo[2,1-b]thiazole (7.8 g., 61.7%) which crystallised from ethanol as colourless plates, m.p. 108-9°, turning green in air.

Found: C,75.27; H,5.93; N,5.73; S,13.16.

$C_{16}H_{15}NS$ requires C,75.85; H,5.97; N,5.53; S,12.65%.

6-Acetyl-3-methylpyrrolo[2,1-b]thiazole.

A solution of 2,4-dimethylthiazole (11.3 g., 0.1 mole) and bromodiacetyl (16.5 g., 0.1 mole) in dry chloroform (50 ml.) was refluxed for 4 hr. The mixture was cooled, extracted with water (2 x 100 ml.) and the aqueous solution washed with ether (4 x 100 ml.). Sodium bicarbonate (28 g., 0.33 mole) was added to the aqueous solution and the mixture heated at 90° for 4 hr. under nitrogen. The mixture was cooled, diluted with water (200 ml.) and extracted with ether. The ether extracts were washed with water, dried (Na_2SO_4), and the solvent evaporated. The brown crystalline residue was sublimed at 0.1 mm. (block temp. 80-5°) and the pale yellow sublimate of 6-acetyl-3-methylpyrrolo[2,1-b]thiazole (2.4 g., 12.2%) recrystallised from acetone - petroleum ether (1:1) as pale yellow needles, m.p. 124-5°.

Found: C,60.86; H,4.96; N,7.59; S,17.31.
C_9H_9NOS requires C,60.31; H,5.06; N,7.82; S,17.89%.

Attempted synthesis of 3-methylpyrrolo[2,1-b]thiazole-6-carboxylic acid.

A solution of ethyl bromopyrurate (58.5 g., 0.3 mole) and 2,4-dimethylthiazole (33.9 g., 0.3 mole.) in dry ethanol (450 ml.) was heated at 100° for 4 hr. and then allowed to stand at room temperature for 96 hr. The ethanol was distilled off at reduced pressure, the residue taken up in water (250 ml.) and the solution extracted three times with chloroform and finally with ether. Sodium bicarbonate was added until effervescence ceased and the mixture extracted with ether. A further portion of sodium bicarbonate (25 g., 0.3 mole) was added and the

mixture heated at 100° for 4 hr. The resulting solution while still warm, was acidified with 2N sulphuric acid and the resinous black precipitate (7 g.) filtered off.

The product was dissolved in methanol (130 ml.) and dry hydrogen chloride gas passed in until a 2% gain in weight was achieved. The mixture was allowed to stand at room temperature for 72 hr., poured into water (2 l.) and extracted with ether. The ether extract was washed with water, dilute potassium carbonate solution, again with water, and dried (Na_2SO_4). Evaporation of the ether and distillation of the residue at 0.1 mm. (block temp. 110-15°) afforded a partially crystallised oil (0.025 g.). Examination of this product by gas-liquid chromatography showed it to consist of several components.

c) Synthesis of pyrrolo[2,1-b]thiazoles from substituted 2-n propylthiazoles.

Attempted synthesis of ethyl-4-phenylthiazol-2-ylpyruvate.

a) To a solution of potassium ethoxide in ether-ethanol, prepared from potassium (7.8 g., 0.2 mole), ether (35 ml.) and ethanol (50 ml.), was added diethyl oxalate (14.6 g., 0.1 mole) and, after 30 min., 2-methyl-4-phenylthiazole (17.4 g., 0.1 mole). The mixture was allowed to stand at room temperature for 24 hr., poured into water (400 ml.) and extracted with ether. Acidification of the aqueous phase afforded no material and the ether extract after drying (Na_2SO_4) and evaporation of the solvent afforded a mixture of reactants.

b) To a suspension of anhydrous potassium tertbutoxide (22.4 g., 0.2 mole) in dry benzene (100 ml.) was added diethyl oxalate (14.6 g., 0.1 mole) and, after 30 min., 2-methyl-4-phenylthiazole (17.4 g., 0.1 mole). The mixture was stirred at room temperature for 24 hr. and worked up in the same manner as in the previous experiment, identical results being obtained.

Reduction of ethyl 2-benzothiazolylpyruvate.

a) To a suspension of the potassium enolate of ethyl 2-benzothiazolylpyruvate[32] (28.7 g.,0.1 mole) in methanol (50 ml.) at room temperature was added a solution of sodium borohydride (4.5 g., 1.5 equivalents) in methanol (150 ml.) and the mixture refluxed for 3 hr. The methanol was distilled off at reduced pressure and the residue treated with 6N sodium hydroxide solution (100 ml.). The mixture was extracted with chloroform, the chloroform extract washed with water, dried (Na_2SO_4) and the solvent

evaporated affording a yellow oil (0.017 g.). The alkaline solution was acidified with acetic acid and the unchanged ethyl 2-benzothiazolylpyrurate (20.1 g., 81%) filtered off and recrystallised from methanol as yellow prisms, m.p. and mixed m.p. 166-8°.

b) To a suspension of ethyl 2-benzothiazolylpyruvate (2.49 g., 0.01 mole.) in methanol (100 ml.), at room temperature, was added portionwise sodium borohydride (0.43 g., 1.5 equivalents) and the mixture refluxed for 1 hr. The methanol was distilled off at reduced pressure and the residue treated with 2N sodium hydroxide solution (40 ml.) and worked up as described in the previous experiment. Evaporation of the chloroform extract afforded a viscous brown oil (1.1 g.) which displayed infra-red hydroxyl and ester carbonyl absorption and which decomposed on attempted distillation. Unchanged ester (0.9 g., 36%) was recovered from the alkaline solution.

c) Ethyl 2-benzothiazolylpyruvate (2.49 g., 0.1 mole.) was reduced with lithium aluminium hydride (0.43 g., 1.5 equivalents) in tetrahydrofuran (200 ml.) using the Soxhlet extraction technique. After the ester had been dissolved the mixture was refluxed for 3 hr., cooled, poured into water (1 l.), neutralised with dilute sulphuric acid and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4) and the solvent evaporated affording an amorphous yellow brown solid (1.45 g.). It slowly decomposes >120°.

The product could not be recrystallised satisfactorily and decomposed on attempted sublimation at reduced pressure. It displayed infra-red carbonyl absorption, gave an orange-

red colouration with Ehrlichs reagent and a green colouration with ethanolic ferric chloride solution.

Syntheses utilising 2-thiazolyl metal compounds.

nButyl lithium[38]

In a 500 ml. flask equipped with a stirrer, dropping funnel and nitrogen inlet was placed anhydrous ether (200 ml.). The apparatus was flushed with nitrogen and lithium (8.8 g., 1.25 g. atom) introduced as small pieces by cutting strips of the metal in a stream of nitrogen above a neck of the flask so that the lithium fell into the ether. Stirring was commenced and 30 drops of a solution of n butyl bromide (68.5 g., 0.5 mole) in anhydrous ether (100 ml.) added to the contents of the flask. The flask was cooled in a bath at -25° to -30° and when the reaction had started, as evidenced by the appearance of bright spots on the metal and a cloudiness in the ether, the remainder of the nbutyl bromide solution was added over 30 min., the cooling bath being maintained at -25° to -30°. After the addition was complete the reaction mixture was allowed to warm up to 0° in the cooling bath and stirring continued for 2 hr. at 0° to 10°. Finally stirring was stopped and the mixture allowed to stand for 30 min. at 0°-10°.

The concentration of the reagent thus prepared was estimated by titration of 5 ml. portions, after treatment, with benzyl chloride (1 ml.) in ether (20 ml.) followed by water (20 ml.), and with water (30 ml.) alone, using 0.5N acid with phenolphthalein as indicator. The difference in quantities of acid used is equivalent to the n butyl lithium present. Yield 85-90%.

2-Thiazolyl lithium[12]

A solution of n butyl lithium (0.275 mole) prepared as described above was transferred by pipette to an apparatus identical to that used in the preparation, which had been previously flushed with nitrogen. The solution was cooled to -40° and a solution of 2-bromothiazole (41 g., 0.25 mole) in ether (50 ml.) was added dropwise over 15 min., the temperature of the reaction mixture being maintained at -40°. The mixture was stirred for 15 min., the temperature being allowed to rise to -30°.

Reaction of 2-thiazolyl lithium with acrolein.

To a stirred solution of 2-thiazolyl lithium (from 0.25 mole 2-bromothiazole), at -30°, was added a solution of acrolein (14 g., 0.25 mole) in ether (35 ml.) dropwise over 25 min. The mixture was stirred for 45 min., the temperature being allowed to rise to -15° and stirring continued at that temperature for 1 hr. The reaction mixture was poured into 5% ammonia solution (1 l.) and extracted with benzene. The benzene extract was washed with water until free of ammonia, dried (K_2CO_3), and the solvent evaporated. The residual brown viscous oil (9.35 g.) was distilled at reduced pressure affording the alcohol as a yellow-green oil (5.94 g.), b.p. 82-8°/0.1 mm., a large quantity of red polymeric material remaining in the distillation flask. Analysis of the product by G.L.C. showed the presence of three components which were closely separated.

Reaction of 2-thiazolyl lithium with methyl vinyl ketone.

To a stirred solution of 2-thiazolyl lithium (from 0.25 mole 2-bromothiazole) at -30° was added a solution of

methyl vinyl ketone (19.25 g., 0.275 mole) in ether (40 ml.) dropwise over 40 min., the temperature being maintained at -30°. The mixture was stirred for 1 hr., the temperature being allowed to rise to -10° and stirring continued at that temperature for 1 hr. The mixture was added to 5% ammonia solution (1 l.) and extracted with benzene. The benzene extract was washed with water until free of ammonia, dried (K_2CO_3), and the solvent evaporated. The residual red oil (14.2 g.) was distilled at reduced pressure two fractions being collected:

b.p. 60-70°/0.1 mm. (9.3 g.) yellow liquid possessing strong infra-red carbonyl absorption which was discarded.

b.p. 106-14°/0.1 mm. (1.1 g.) yellow viscous oil possessing strong infra-red hydroxyl absorption and which was shown to consist of at least three components with close boiling points by G.L.C.

A small amount of a red polymeric residue remained in the distillation flask.

Reaction of 2-thiazolyl magnesium bromide with crotonaldehyde.

A mixture of 2-bromothiazole (32.8 g., 0.2 mole) and ethyl bromide (44 g., 0.4 mole) was added with stirring to magnesium (15 g., 0.6 g.atom) in ether (100 ml.) at such a rate that the ether refluxed gently. (Reaction was initiated by a few drops of ethyl bromide.). When the addition was complete the mixture was refluxed for 1 hr. The Grignard reagent was cooled in ice and a solution of crotonaldehyde (42 g., 0.6 mole) in ether (100 ml.) added dropwise over 1 hr. with stirring. After the addition was complete, the mixture was refluxed for 1 hr., cooled, and hydrolysed by pouring into 5% ammonium sulphate solution

(1 l.) containing ice (300 g.). The mixture was extracted with ether, the ether extract washed well with water, dried (K_2CO_3), and the solvent evaporated. The residual red oil was distilled at reduced pressure affording 4-hexen-3-ol (27 g., 68%), b.p. 46-7°/13 mm. (Lit.[33] b.p. 44-7°/12 mm.). The residue was taken up in ether, dried (K_2CO_3), the solvent evaporated and the red oily residue distilled at reduced pressure affording a fraction (19 g), b.p. 92-9°/0.1 mm. which was shown by G.L.C. to contain at least three compounds of very similar volatility.

Attempted cyclisaton of the 2-thiazolyl vinyl carbinols.

Attempts were made to cyclise the products of the previous three reactions to pyrrolo[2,1-b]thiazoles using the reagents listed below. In each case the product was extracted by basification of the reaction mixture, steam distillation and extraction of the distillate with ether.

a) 0.5 N Sulphuric acid.
b) 0.05 N Sulphuric acid.
c) Glacial acetic acid.
d) Acetic anhydride.
e) 9 N Hydrobromic acid followed by alkali.
f) 50% Hydrogen bromide in acetic acid followed by alkali.

In each case a variety of reaction times and temperatures were used. The ether extract in all cases contained material affording a positive reaction with Ehrlich's reagent but never in sufficient quantity to permit its isolation as a perchlorate or picrate.

Reaction of 2-thiazolyl lithium with 3-ethoxypropionitrile.

To a stirred solution of 2-thiazolyl lithium, (from 0.25 mole 2-bromothiazole) at -30°, was added a solution of

3-ethoxypropionitrile (27.5 g., 0.275 mole) in ether (40 ml.) dropwise over 40 min., the temperature of the reaction mixture being maintained at -30° during the addition. The mixture was stirred for 30 min., the temperature being allowed to rise to -15° and stirring continued at this temperature for 1 hr. The cooling bath was then removed and stirring continued for a further 1 hr. at room temperature. The reaction mixture was poured into 2N hydrochloric acid (1.1.), after standing at room temperature for 1 hr. the mixture was made alkaline with ammonia and extracted with ether. The ether extract was washed with water until free of ammonia and dried (Na_2SO_4). Evaporation of the ether and distillation of the residual red oil at reduced pressure afforded a material (2.1 g.), b.p. 55-65°/0.1 mm. presumably n butyl 2-ethoxyethyl ketone. A large quantity of a red polymeric residue remained in the distillation flask.

Reaction of 2-thiazolyl magnesium bromide with 3- ethoxypropionitrile.

A mixture of 2-bromothiazole (16.4 g., 0.1 mole) and ethyl bromide (22 g., 0.2 mole) was added with stirring to magnesium (7.5 g., 0.3 g.atoms) in ether (50 ml.) at such a rate that the ether refluxed gently. (Reaction was initiated by a few drops of ethyl bromide.) When the addition was complete the mixture was refluxed for 1 hr., cooled in ice, and a solution of 3-ethoxypropionitrile (29.7 g., 0.3 mole) in ether (50 ml.) added dropwise over 45 min. with stirring. After completion of the addition the mixture was refluxed for 1 hr., cooled in ice and a solution of ammonium sulphate (40 g.) in water (150 ml.)

added slowly with stirring. The mixture was then gently warmed so that the ether refluxed for one hour, cooled, basified with ammonia and extracted with ether. A large quantity of ether-insoluble red gum was discarded, the ether solution washed with water until free of ammonia and dried (Na_2SO_4). Evaporation of the solvent and distillation of the residual red oil afforded a material (18.7 g.), b.p. 65-70°/10 mm. presumably 1-ethoxypentan-3-one (Lit.[34] b.p. 45°/3 mm. A large quantity of a red polymeric material remained in the distillation flask.

Reaction of 2-thiazolyl lithium with 3-ethoxypropionaldehyde.

To a stirred solution of 2-thiazolyl lithium (from 0.25 mole 2-bromothiazole) at -30° was added a solution of 3-ethoxypropionaldehyde[35] (28 g., 0.275 mole) in ether (40 ml.), dropwise over 30 min., the temperature of the reaction mixture being maintained at -30° during the addition. The mixture was stirred for 30 min. the temperature being allowed to rise to -15° and stirring continued at that temperature for 1 hr. The cooling bath was removed and the mixture allowed to stand for 2 hr. at room temperature. The mixture was hydrolysed by pouring into a solution of ammonium sulphate (100 g.) in water (1 l.), the mixture was shaken for 5 min., made alkaline with ammonia and extracted with ether. The ether solution was washed with water until free of ammonia and dried (K_2CO_3). The solvent was evaporated and the red oily residue distilled at reduced pressure, two fractions being collected:

b.p. 80-85°/0.1 mm. (3.4 g.) presumably 1-ethoxyheptan-3-ol.

b.p. 97-98°/0.1 mm. (32 g., 68%) of 3-ethoxy-1-(2-thiazolyl)-propanol.

Found: C,51.62; H,7.19.

$C_8H_{13}NO_2S$ requires C,51.34; H,6.95%.

Attempted cyclisation of 3-ethoxy-1-(2-thiazolyl)-propanol.

The alcohol was treated with 9% hydrobromic acid and also with 50% hydrogen bromide in acetic acid followed in each case by treatment with alkali, steam distillation, etc. In both cases sufficient pyrrolo[2,1-b] thiazole was produced to give a positive reaction with Ehrlichs reagent but not to allow isolation as a perchlorate or picrate.

Reaction of 2-thiazolyl lithium with 3-chloropropionaldehyde.

To a stirred solution of 2-thiazolyl lithium (from 0.25 mole 2-bromothiazole) at -30° was added a solution of freshly prepared 3-chloropropionaldehyde[36] (25.6 g., 0.275 mole) in ether (40 ml.), dropwise over 30 min., the temperature of the reaction mixture being maintained at -30° during the addition. The mixture was stirred for 30 min., the temperature being allowed to rise to -20°, and stirring continued for 1 hr. at this temperature. The cooling bath was then removed and the mixture allowed to stand at room temperature for 12 hr. The reaction mixture was poured into water (1 l.), concentrated ammonia solution (50 ml.) added and the mixture extracted with ether, a large quantity of ether-insoluble sticky black polymer being discarded. The ether solution was washed with water until free off ammonia and dried (Na_2SO_4). Evaporation of the solvent afforded a brown oil (36.5 g.) which could not be purified by distillation as on heating a

vigorous reaction occured to give a solid polymeric resin.

Attempted cyclisation of the crude 3-chloro-1-(2-thiazolyl)-propanol.

Attempts were made to cyclise the crude product from the previous reaction using the reagents listed below under a variety of conditions. In all cases the base was isolated by basification of the reaction mixture, steam distillation and ether extraction of the distillate.

a) 9N Hydrobromic acid followed by alkali.
b) Boiling ethanol.
c) Formamide at 100°.
d) Boiling acetic acid.
e) Boiling tert butanol.

In all cases the ether extract contained material which gave a very faint positive reaction with Ehrlichs reagent.

Reaction of 2-thiazolyl lithium with 3-methoxyepoxypropane.

To a stirred solution of 2-thiazolyl lithium (from 0.25 mole 2-bromothiazole) at -30° was added a solution of 3-methoxyepoxypropane[39] (24.5 g., 0.275 mole) in ether (50 ml.) dropwise over 30 min., the temperature of the reaction mixture being maintained at -30° during the addition. The mixture was stirred for 40 min. the temperature being allowed to rise to -15° and stirring continued for 1 hr. at this temperature. The cooling bath was removed and the mixture allowed to stand at room temperature for 1 hr. The reaction mixture was poured into a solution of ammonium sulphate (60 g.) in water (1 l.) and the mixture allowed to stand for 1 hr. before being made alkaline with ammonia and extracted with ether.

The ether solution was washed with water until free of ammonia and dried (K_2CO_3). Evaporation of the ether afforded a red oil which was distilled at reduced presure, two fractions being collected.

a) b.p. 54-6°/0.1 mm.,(5.7 g.) presumably 1-methoxyheptan-2-ol.

b) b.p. 102-10°/0.1 mm., (1.3 g.) impure 3-methoxy-1-(2-thiazolyl)-propan-2-ol, as a dark yellow oil.

A considerable amount of solid black polymer remained in the distillation flask.

Attempted cyclisation of the crude 3-methoxy-1-(2-thiazolyl)-propan-2-ol.

The impure alcohol was treated with 9N hydrobromic acid followed by alkali and the products isolated by steam distillation and ether extraction of the distillate. The ether extract contained only sufficient pyrrolo [2,1-b] thiazole to afford a weakly positive reaction with Ehrlichs reagent.

Reaction of 2-thiazolyl lithium with epichlorohydrin.

To a stirred solution of 2-thiazolyl lithium (from 0.4 mole 2-bromothiazole) at -30° was added a solution of epichlorohydrin (41 g., 0.4 mole) in ether (70 ml.) dropwise over 30 min., the temperature of the reaction mixture being maintained at -30° during the addition. The mixture was stirred for 45 min., the temperature being allowed to rise to -15°, and stirring continued for 1 hr. at this temperature followed by 1 hr. at room temperature. The reaction mixture was poured into a solution of ammonium sulphate (80 g.) in water (1.5 l.) allowed to stand at room temperature for 1 hr. and the mixture made alkaline

with ammonia. The product was extracted with ether, the ether solution washed with water until free of ammonia, and dried (Na_2SO_4). Evaporation of the ether afforded the crude 1-(2-thiazolyl)-3-chloropropan-2-ol as a red oil (42 g.) which could not be purified by distillation as on heating it polymerised to a crimson solid.

Pyrrolo[2,1-b]thiazole.

A solution of crude 1-(2-thiazolyl)-3-chloropropan-2-ol (42 g., from 0.4 mole 2-bromothiazole) in tert butanol (420 ml.) was refluxed for 6 hr. After cooling the mixture was diluted with water (1 l.), made alkaline by the addition of solid potassium carbonate, and steam distilled. The distillate was extracted with ether, the ether solution was washed well with water, dried (K_2CO_3), and the solvent evaporated. Distillation of the residual yellow oil at 10 mm. (block temp. 80-5°) afforded pyrrolo[2,1-b]thiazole (0.93 g., 1.9% from 2-bromothiazole) as a pale yellow oil which rapidly became black in air.

d) Syntheses of pyrrolo[2,1-b]thiazoles involving closure of the thiazole ring.

Thioxindole.

A mixture of oxindole[16] (8 g., 0.06 mole) and phosphorus pentasulphide (4 g., 0.018 mole) together with an equal volume of Hyflo Supercel in dry xylene (50 ml.) was heated at 100° for 50 min. The hot solution was filtered and the solid washed with hot (100°) xylene (20 ml.). The combined filtrate and washings on cooling deposited thioxindole (2.35 g., 26%) which crystallised from xylene as bright yellow plates which decompose >142°.

Lit.[16] decomposes >145°.

3-Phenylbenzo[e]pyrrolo[2,1-b]thiazole.

A solution of thioxindole (2.25 g., 0.015 mole) and phenacyl bromide (3.0 g., 0.015 mole) in dry ethanol (130 ml.) was allowed to stand at room temperature for 14 hr. The solution, which was initially yellow, became dark red in 20 min. and finally dark green with the deposition of a small quantity of a black solid. The mixture was poured into water (1 l.), potassium carbonate (5 g.) was added, and the mixture was extracted with methylene chloride. The methylene chloride solution was washed with water, dried (Na_2SO_4) and the solvent evaporated. The dark oily residue was distilled at 0.1 mm. (block temp. 160-5°). The distillate, a pale yellow oil (0.015 g.) was dissolved in ethanol (3 ml.), ethyl orthoformate (1 ml.), and perchloric acid (0.1 ml.) added and the mixture boiled for 1 min., 7-(3-phenylbenzo[e]pyrrolo[2,1-b]thiazol-7-yl)-methylene-3-phenylbenzo[e]pyrrolo[2,1-b]thiazolium perchlorate (0.014 g., 0.15% from thioxindole)

crystallised from the solution and was filtered off, washed well with ether and recrystallised from acetonitrile as green needles. It decomposes slowly >300°.

max 617mu (log 5.0346) in acetonitrile containing 1% v/v perchloric acid.

Found: N,4.46; S,10.02.

$C_{33}H_{21}ClN_2O_4S_2$ requires N,4.60; S,10.53%.

Attempted synthesis of 3-methylbenzo[e]pyrrolo[2,1-b] thiazole.

A solution of thioxindole (1.5 g., 0.01 mole) and bromoacetone (1.37 g., 0.01 mole) in dry ethanol (90 ml.) was allowed to stand at room temperature for 15 hr. The solution, which was initially yellow, became brown in 30 min., and finally dark green with the deposition of a small quantity of a black solid. The mixture was poured into water (800 ml.), potassium carbonate (4 g.)was added, and the mixture was extracted with methylene chloride. The methylene chloride solution was washed with water, dried (Na_2SO_4) and the solvent evaporated affording a brown oil (0.03 g.) which did not afford a positive reaction with Ehrlichs reagent.

Ethyl 3,4-dimethyl-5-thiocyanopyrrole-2-carboxylate.

To a solution of ethyl 3,4-dimethylpyrrole-2-carboxylate[37] (8.35 g., 0.05 mole) in dry methanol (400 ml.) was added cupric thiocyanate (17.6 g., 0.1 mole) and the mixture allowed to stand at room temperature for 1 hr. with occasional shaking. The cuprous thiocyanate was filtered off and washed with methanol (100 ml.). The combined filtrate and washings were poured into water (1.5 l.) and the precipitated ethyl 3,4-dimethyl-5-thio-

cyanopyrrole-2-carboxylate (8.95 g., 80%) filtered off, dried in vacuo and recrystallised from petroleum ether as colourless silky needles, m.p. 160.5-2.5° (sublimes >130°).

Found: N,12.18.

$C_{10}H_{12}N_2O_2S$ requires N,12.49%.

Attempted preparation of ethyl 5-mercapto-3,4-dimethyl-pyrrole-2-carboxylate.

To a solution of ethyl 3,4-dimethyl-5-thiocyano-pyrrole-2-carboxylate (0.448 g., 2 mole) in glacial acetic acid (20 ml.) was added freshly cleaned zinc wool (1 g.), the mixture refluxed for 5 min., poured into water (500 ml.) and the mixture extracted with ether. The ether solution was washed with water and dried ($MgSO_4$). Evaporation of the solvent afforded a yellow crystalline residue (0.3 g.), m.p. 125-70° which was partially soluble in light petroleum.

Attempted reaction of the unstable ethyl 5-mercapto-3,4-dimethylpyrrole-2-carboxylate with phenacyl bromide.

The solution from a reduction as described above was decanted from the zinc wool which was washed with glacial acetic acid (10 ml.) and the washings added to the solution. Phenacyl bromide (0.398 g., 2 mmole) was added and the mixture allowed to stand at room temperature for 4 hr. The resulting solution was poured into water (1 l.) and the mixture extracted with ether. The ether solution was washed with water, dried ($MgSO_4$) and the solvent evaporated. The residual brown oil (0.7 g.), smelling strongly of phenacyl bromide gave a negative reaction with Ehrlichs reagent.

CIII. Properties of pyrrolo[2,1-b]thiazoles.

a) Trinitrobenzene complexes of pyrrolo[2,1-b]thiazoles.

General Procedure.

To a solution of the pyrrolo[2,1-b]thiazole (0.5 mmole) in cold ethanol (2 ml.) was added a solution of trinitrobenzene (0.107 g., 0.5 mmole) in the minimum volume of boiling ethanol. The mixture was cooled to room temperature, the complex filtered off and recrystallised from ethanol.

Pyrrolo[2,1-b]thiazole afforded orange-red needles (66%), m.p. 124-7° (with decomposition).

Found: N, 17.08

$C_{12}H_8N_4O_6S$ requires N,16.67%.

6-Methylpyrrolo[2,1-b]thiazole afforded crimson needles (79%), m.p. 121.5-4°.

Found: N,16.36.

$C_{13}H_{10}N_4O_6S$ requires N,15.99%.

2,6-Dimethylpyrrolo[2,1-b]thiazole afforded bright red needles (80%), m.p. 125.5-8° (with decomposition, softens >121°).

Found: N,14.98.

$C_{14}H_{12}N_4O_6S$ requires N,15.38%.

3,6-Dimethylpyrrolo[2,1-b]thiazole afforded deep red needles (82%), m.p. 123-5° (softens >115°).

Found: N,15.20.

$C_{14}H_{12}N_4O_6S$ requires N,15.38%.

5,6-Dimethylpyrrolo[2,1-b]thiazole afforded brown needles (77%), m.p. 124-7° (with decomposition).

Found: C,45.77; H,3.16; N,15.44; S,9.86.

$C_{14}H_{12}N_4O_6S$ requires C,46.13; H,3.29; N,15.38; S,8.79%.

6,7-Dimethylpyrrolo[2,1-b]thiazole afforded brown needles (82%) which decompose slowly to a black liquid >135°.

Found: N,15.12.

$C_{14}H_{12}N_4O_6S$ requires N,15.38%.

2,6,7-Trimethylpyrrolo[2,1-b]thiazole afforded brown needles (89%) which decompose slowly to a black liquid >130°.

Found: N,15.14.

$C_{15}H_{14}N_4O_6S$ requires N,14.81%.

5,6,7-Trimethylpyrrolo[2,1-b]thiazole afforded dark brown needles (93%), m.p. 149-52°. (with decomposition to a black liquid).

Found: N,15.25.

$C_{15}H_{14}N_4O_6S$ requires N,14.81%.

6-Methyl-2,3-tetramethylenepyrrolo[2,1-b]thiazole afforded deep red needles (84%), m.p. 121-2°.

Found: N,13.79.

$C_{17}H_{16}N_4O_6S$ requires N,13.88%.

b) Pyrrolo[2,1-b]thiazolium salts.

1) Picrates.

General Procedure.

To a solution of the pyrrolo[2,1-b]thiazole (0.5 mmole) in cold ethanol (1 ml.) was added a solution of picric acid (0.115 g., 0.5 mmole) in the minimum volume of boiling ethanol. The mixture was cooled to room temperature, the salt filtered off and recrystallised

from ethanol.

6-Methylpyrrolo[2,1-b]thiazolium picrate was obtained as yellow needles (97%), m.p. 155-60° (with decomposition).

Found: N,14.72.

$C_{13}H_{10}N_4O_7S$ requires N,15.30%.

5,6-Dimethylpyrrolo[2,1-b]thiazolium picrate was obtained as yellow needles (80%), m.p. 105-13° (with decomposition).

Found: C,43.74; H,3.06; N,14.50.

$C_{14}H_{12}N_4O_7S$ requires C,44.21; H,3.18; N,14.73%.

5,6,7-Trimethylpyrrolo[2,1-b]thiazolium picrate was obtained as yellow prisms (64%), m.p. 130-3° (darkens >115°).

Found: N,14.22.

$C_{15}H_{14}N_4O_7S$ requires N,14.21%.

2) Perchlorates.

General procedure.

To a solution of the pyrrolo[2,1-b]thiazole (0.5 mmole) in ethanol (5 ml.) at room temperature was added perchloric acid (0.6 ml., 34% excess). The solution was cooled and the pyrrolo[2,1-b]thiazolium perchlorate filtered off, washed with a little ethanol followed by ether and unless otherwise stated recrystallised from ethanol.

Pyrrolo[2,1-b]thiazolium perchlorate was obtained as colourless needles (93%) which very rapidly became violet under the influence of light, using methanol (5 ml.) as solvent. The material could not be recrystallised satisfactorily and an analytical sample was prepared directly using filtered solutions. It decomposes without melting at 200-230° to a black liquid.

Found: C,33.64; H,2.72; N,5.67.

$C_6H_6ClNO_4S$ requires C,32.14; H,2.68; N,6.25%.

6-Methylpyrrolo[2,1-b]thiazolium perchlorate was obtained as colourless needles (97%), m.p. 122.75-3.75°.

Found: C,35.29; H,3.29; N,5.91; S,13.32.

$C_7H_8ClNO_4S$ requires C,35.37; H,3.39; N,5.89; S,13.49%.

6-Phenylpyrrolo[2,1-b]thiazolium perchlorate was obtained as colourless needles (88%) using hot (60-70°) glacial acetic acid (5 ml.) as solvent. The material decomposed on attempted recrystallisation and a sample for analysis was prepared directly using filtered solutions, m.p. 169-71°.

Found: N,5.14.

$C_{12}H_{10}NO_4SCl$ requires N,4.67%.

2,6-Dimethylpyrrolo[2,1-b]thiazolium perchlorate was obtained as colourless needles (97%), m.p. 137.5-9°.

Found: C,38.05; H,4.52; N,5.55; S,12.81.

$C_8H_{10}ClNO_4S$ requires C,38.18; H,4.29; N,5.57; S,12.74%.

3,6-Dimethylpyrrolo[2,1-b]thiazolium perchlorate was obtained as colourless needles (95%), m.p. 133.5-5°.

Found: C,38.54; H,4.01; N,5.83; S,13.18.

$C_8H_{10}ClNO_4S$ requires C,38.18; H,4.29; N,5.57; S,12.74%.

6,7-Dimethylpyrrolo[2,1-b]thiazolium perchlorate was obtained as colourless needles (96%), m.p. 178-81° (decomposes to a red liquid).

Found: C,38.31; H,3.80; N,5.24; S,12.06.

$C_8H_{10}ClNO_4S$ requires C,38.18; H,4.29; N,5.57; S,12.74%.

2-Methyl-6-phenylpyrrolo[2,1-b]thiazolium perchlorate was

obtained as pale yellow needles (94%) using hot (65°) ethanol (40 ml. for 1 mmole) as solvent and was recrystallised from ethanol containing 1% (v/v) perchloric acid, m.p. 172-5°.

Found: N,4.06.

$C_{13}H_{12}ClNO_4S$ requires N,4.47%.

3-Methyl-6-phenylpyrrolo[2,1-b]thiazolium perchlorate was obtained as colourless needles (95%) using cold acetonitrile (5 ml. for 1 mmole) as solvent and was recrystallised from acetonitrile containing 1% (v/v) perchloric acid, m.p. 210-16°, (with decomposition, softens at >200°).

Found: N,4.96.

$C_{13}H_{12}ClNO_4S$ requires N,4.47%.

3,6,7-Trimethylpyrrolo[2,1-b]thiazolium perchlorate was obtained as colourless needles (97%), m.p. 109.5-12° (softens >105°.).

Found: C,40.69; H,4.68; N,5.11; S,11.65.

$C_9H_{12}ClNO_4S$ requires C,40.68; H,4.55; N,5.27; S,12.07%.

5,6,7-Trimethylpyrrolo[2,1-b]thiazolium perchlorate was obtained as colourless prisms (94%), m.p. 151-3°, (softens >140°)

Found: C,40.70; H,4.05; N,5.24; S,12.50.

$C_9H_{12}ClNO_4S$ requires C,40.68; H,4.55; N,5.27; S,12.07%.

6-Phenylbenzo[b]pyrrolo[2,1-b]thiazolium perchlorate was obtained as pale yellow prisms (99%) using hot (65°) acetonitrile (5 ml. for 1 mmole) as solvent with ether (10 ml.) to precipitate the salt. The product could not be recrystallised satisfactorily and a sample for analysis was prepared directly using filtered solutions, m.p. 225-8° (with decomposition.).

Found: N,4.17.

$C_{16}H_{12}ClNO_4S$ requires N,4.00%.

2,6-Dimethyl-7-phenylpyrrolo[2,1-b]thiazolium perchlorate was obtained as colourless needles (97%), m.p. 155-7.5°.

Found: C,50.90; H,4.68; N,4.27; S,10.19.

$C_{14}H_{14}ClNO_4S$ requires C,51.30; H,4.31; N,4.27; S, 9.78%.

6-Methyl-2,3-tetramethylenepyrrolo[2.1-b]thiazolium perchlorate was obtained as colourless plates (98%),m.p. 157-9.5°.

Found: C,45.64; H,4.66; N,4.67; S,11.37.

$C_{11}H_{14}ClNO_4S$ requires C,45.28; H,4.84; N,4.80; S,10.99%.

6-Phenyl-2,3-tetramethylenepyrrolo[2.1-b]thiazolium perchlorate was obtained as pale yellow prisms (96%) using hot (65°) ethanol (5 ml. for 1 mmole) as solvent and was recrystallised from glacial acetic acid, m.p. 256-9°, (with decomposition).

Found: N,3.74.

$C_{16}H_{16}ClNO_4S$ requires N,3.96%.

CIV Substitution reactions of pyrrolo[2,1-b]thiazoles

a) Examination of the acetylated products from the Chichibabin cyclisation reaction.

Product from 3-acetonyl-2-methylthiazolium bromide.

The crude cyclisation product (1.1 g., from 0.005 mole salt) was dissolved in benzene-ether (60:40; 15 ml.) and chromatographed on alumina (25 cm. x 3.5 cm.diam.). Elution was with benzene-ether mixtures and the fractions were analysed by thin-layer chromatography as below.

Fraction no.	Eluting Volume (ml.).	Solvent. % Ether.	Wt. of material	Analysis
1	250	40	0.008 g.	Low polarity material.
2	375	50	0.226 g.	Monoacetyl compound.
3	375	50	0.227 g.	Diacetyl compound.
4	750	60	0.516 g.	Diacetyl compound.
5	450	70	0.017 g.	More polar material.

The material from fraction 2 was sublimed at 0.1 mm. (block temp. 75-80°) to afford monoacetyl-6-methylpyrrolo[2,1-b]thiazole (0.226 g., 21% of crude, 25% from the salt) as colourless prisms, m.p. 71-4°.

Found: N,7.76.

C_9H_9NOS requires N,7.81%.

The combined material from fractions 3 and 4 was recrystallised from benzene-cyclohexane (1:1) to afford diacetyl-6-methylpyrrolo[2,1-b]thiazole (0.743 g., 68.5% of crude, 65% from the salt) as colourless needles, m.p. 144.5-5.5°. (sublimes >135°)

Found: C,59.87; H,5.28.

$C_{11}H_{11}NO_2S$ requires C,59.73; H,4.97%.

Product from 3-(3-buten-2-onyl)-2-methylthiazolium bromide.

The crude cyclisation product (0.507 g., from 0.003 mole 2-methylthiazole and 3-bromobutan-2-one) was sublimed at 0.1 mm. (block temp. 90-5°). Crystallisation of the sublimate from cyclohexane afforded monoacetyl-5,6-dimethylpyrrolo[2,1-b]thiazole (0.27 g., 53% of crude, 46% from 2-methylthiazole and 3-bromobutan-2-one) as colourless cubes, m.p. 92-3°.

Found: N,7.29.

$C_{10}H_{11}NOS$ requires N,7.25%.

Product from 3-acetonyl-2-ethylthiazolium bromide.

The crude cyclisation product (0.27 g., from 0.0014 mole salt) was sublimed at 0.1 mm. (block temp. 95-100°). Crystallisation of the sublimate from petroleum ether afforded monoacetyl-6,7-dimethylpyrrolo[2,1-b]thiazole (0.246 g., 91% of crude, 90% from the salt) as colourless needles, m.p. 120-1°.

Found: N,6.94.

$C_{10}H_{11}NOS$ requires N,7.25%.

Product from 3-acetonyl-2-ethyl-4-methylthiazolium bromide.

The crude cyclisation product (0.356 g., from 0.0017 mole salt) was sublimed at 0.1 mm. (block temp. 95-100°) affording monoacetyl-3,6,7-trimethylpyrrolo[2,1-b]thiazole (0.343 g., 96.5% of crude, 97% from the salt) as colourless needles, m.p. 50-3°.

Found: N,6.89.

$C_{11}H_{13}NOS$ requires N,6.76%.

b) Acetylation of 6-methylpyrrolo[2,1-b]thiazole.

Using acetic anhydride - sodium acetate.

A solution of 6-methylpyrrolo[2,1-b]thiazole (0.411 g., 3 mmole) and fused sodium acetate (0.492 g., 6 mmole) in acetic anhydride (5 ml.) was refluxed for 2 hr., poured into cold water (70 ml.), the mixture allowed to stand at room temperature for 12 hr. and extracted with methylene chloride. The methylene chloride extract was washed with water, dilute potassium carbonate solution, again with water and was dried (Na_2SO_4). Evaporation of the solvent and distillation of the residual red oil at 0.1 mm. (block temp. 75-80°) afforded monoacetyl-6-methylpyrrolo[2,1-b]thiazole (0.515 g., 96%), as colourless prisms, identical to the cyclisation product, m.p. and mixed m.p. 71-4°.

Using acetic anhydride at reflux temperature.

The reaction described above was carried out with the omission of the sodium acetate. The product (0.521 g., 97%) was identical.

Using acetic anhydride at elevated temperature.

A solution of 6-methylpyrrolo[2,1-b]thiazole (0.543 g., 4 mmole) in acetic anhydride (16 ml.) was heated at 205° for 2 hr. in a sealed tube. The tube and contents were cooled to 0° before opening and the contents poured into cold water (600 ml.). The mixture was allowed to stand at room temperature for 12 hr. and was extracted with methylene chloride. The methylene chloride solution was washed with water, dilute potassium carbonate solution, again with water and was dried (Na_2SO_4). Evaporation of the solvent afforded a brown partially solidified oil

(0.832 g.) which was dissolved in benzene-ether (80:20., 15 ml.) and chromatographed on alumina (30 cm. x 2.5 cm. diam.). Elution was with benzene ether mixtures and the fractions were analysed by thin layer chromatography as below.

Fraction no.	Eluting solvent Volume (ml.).	% Ether	Wt. of material	Analysis.
1	250	20	0.050 g.	Monoacetyl compound.
2	250	20	0.114 g.	Monoacetyl compound.
3	250	20	0.173 g.	Monoacetyl compound.
4	250	20	0.036 g.	Diacetyl compound.
5	250	20	0.084 g.	Diacetyl compound.
6	500	60	0.182 g.	Diacetyl compound.
7	700	80	0.024 g.	Diacetyl compound.

The combined material from fractions 1,2 and 3 was sublimed at 0.1 mm.(Block temp. 75-80°) to afford monoacetyl-6-methylpyrrolo[2,1-b]thiazole (0.337 g., 47%), as colourless prisms, identical to the cyclisation product, m.p. and mixed m.p. 71-4°.

The combined material from fractions 4,5,6 and 7 was crystallised from benzene-cyclohexane (1:1) to afford diacetyl-6-methylpyrrolo[2,1-b]thiazole (0.322 g., 36%), as colourless needles, identical to the cyclisation product, m.p. and mixed m.p. 144.5-5.5°.

Using acetic anhydride - perchloric acid.

A solution of 6-methylpyrrolo[2,1-b]thiazolium per-

chlorate (0.474 g., 2 mmole) in acetic anhydride (10 ml.) was refluxed for 1 hr. The resulting dark violet solution was poured into water (500 ml.), the mixture allowed to stand at room temperature for 12 hr. before being extracted with methylene chloride. The methylene chloride extract was washed with water, dilute potassium carbonate solution, again with water and was dried (Na_2SO_4). Evaporation of the solvent afforded a black solid (0.348 g.) which was analysed by thin layer chromatography, this showed the presence of traces of mono- and diacetyl-6-methylpyrrolo[2,1-b]thiazole together with more polar material forming a streak from the origin.

Using acetic anhydride - stannic chloride.

1) A solution of 6-methylpyrrolo[2,1-b]thiazole (0.274 g., 2 mmole) and anhydrous stannic chloride (2.08 g., 8 mmole) in acetic anhydride (10 ml.) was allowed to stand at room temperature for 24 hr. The resulting mixture was poured into water (100 ml.) and the mixture allowed to stand at room temperature for 12 hr. before being extracted with chloroform. The chloroform solution was washed with water, dilute potassium carbonate solution, again with water and was dried (Na_2SO_4). Evaporation of the solvent afforded a brown oil (0.304 g.) which was analysed by thin layer chromatography, this showed the presence of unchanged base (ca. 40%), monoacetyl-6-methylpyrrolo[2,1-b]thiazole (ca. 10%), a trace of diacetyl-6-methylpyrrolo[2,1-b]thiazole together with more polar compounds forming a streak from the origin.

2) The previous experiment was repeated, the solution being refluxed for 2 hr. The product (0.32 g.) contained

no unchanged base, monoacetyl- or diacetyl-compound but consisted of very polar materials retained at or near the origin of the chromatogram.

c) Nitration.

Nitration of 6-methylpyrrolo[2,1-b]thiazole.

Using cupric nitrate - acetic anhydride.

To a solution of cupric nitrate trihydrate (0.645 g., 2.67 mmole) in acetic anhydride (16 ml.) was added 6-methylpyrrolo[2,1-b]thiazole (0.274 g., 2 mmole). The mixture was allowed to stand at room temperature for 1.5 hr., poured into cold water (400 ml.), the mixture neutralised by the addition of solid potassium carbonate and then extracted with methylene chloride, a large quantity of tarry, methylene chloride insoluble material being discarded at this stage. The methylene chloride extract was washed with water, dried (Na_2SO_4) and the solvent evaporated. Analysis of the black amorphous residue (0.08 g.) by thin layer chromatography showed the presence of only very polar material in a streak from the origin of the chromatogram.

Using tetranitromethane.

To a solution of 6-methylpyrrolo[2,1-b]thiazole (0.685 g., 5 mmole) in dry pyridine (55 ml.) was added a solution of tetranitromethane (0.97 g., 5 mmole) in anhydrous ethanol (20 ml.). The solution became red on mixing and warmed slightly, rapidly becoming dark green. After 10 min. at room temperature ether (400 ml.) was added and the solution washed five times with water, three times with 0.5 N sulphuric acid, three times with water

and was dried ($MgSO_4$). The ether solution was concentrated to ca.100 ml. by distillation and chromatographed on neutral alumina (17 cm. x 2.8 cm. diam.), two 1 l. portions of ether being used for elution. Evaporation of the first fraction afforded an orange solid (0.35 g.) which was recrystallised from carbon tetrachloride as orange needles, m.p. 84.5 - 6°.

Found: C,51.15; H,3.17; N,14.21; S,18.40.
$C_{14}H_{11}N_3O_3S_2$ requires C,50.45; H,3.30; N,12.61; S,19.22%.

Evaporation of the second fraction afforded a brown oil (0.05 g.) which was shown by thin layer chromatography to contain at least six compounds all more polar than the material isolated from the first fraction.

Attempted nitration of monoacetyl-6-methylpyrrolo[2,1-b] thiazole.

Using cupric nitrate - acetic anhydride.

1) To a solution of cupric nitrate trihydrate (0.323 g., 1.33 mmole) in acetic anhydride (8 ml.) was added monoacetyl-6-methylpyrrolo[2,1-b]thiazole (0.179 g., 1 mmole). The mixture was allowed to stand at room temperature for 1.5 hr., poured into cold water (400 ml.) and the mixture neutralised by theaddition of solid potassium carbonate. The mixture was extracted with methylene chloride, the extract was washed with water, dried ($MgSO_4$) and the solvent evaporated. Examination of the brown amorphous residue (0.163 g.) by thin layer chromatography indicated the presence of a trace ofstarting material together with a large amount of very polar material formin a streak from the origin of the chromatogram.

2) The above reaction was repeated, the reaction mixture being shaken vigorously at room temperature for 10 min. The product, a brown tar (0.11 g.) was analysed by thin layer chromatography and found to contain starting material (ca. 40%) the remainder of the product forming a streak from the origin of the chromatogram.

Using tetranitromethane.

1) To a solution of monoacetyl-6-methylpyrrolo[2,1-b] thiazole (0.09 g., 0.5 mmole) in dry pyridine (5 ml.) was added a solution of tetranitromethane (0.098 g., 0.5 mmole) in anhydrous ethanol (2 ml.). The mixture was allowed to stand at room temperature for 10 min., diluted with ether (200 ml.) and the resulting solution washed five times with water, three times with 0.5N sulphuric acid, two times with water and dried (Na_2SO_4). The solution was concentrated to ca. 50 ml. by distillation and filtered through a column of neutral alumina (10 cm. x 2.5 cm. diam.) using ether (750 ml.) as eluant. Evaporation of the solvent afforded a pale yellow solid (0.098 g.), analysis by thin layer chromatography showed that this consisted of unreacted starting material together with traces of two more polar yellow compounds.

2) The previous reaction was repeated using a reaction time of 12 hr. The product (0.09 g.) was a pale yellow solid which was shown by thin layer chromatography to be identical to the product obtained from the previous experiment except for a slight increase in the amounts of the two yellow compounds.

d) Formylation of 6-methylpyrrolo[2,1-b]thiazole.

Vielsmeier method.

To a stirred solution of 6-methylpyrrolo[2,1-b] thiazole (0.685 g., 5 mmole) in anhydrous dimethylformamide (7 ml.) cooled in a solid carbon dioxide-acetone bath at -35° to -40° was added a solution of phosphorus oxychloride (0.847 g., 5.5 mmole) in anhydrous dimethylformamide (5 ml.) dropwise over 30 min. The solution became green and finally pale violet, the cooling bath was allowed to warm to 0°, the mixture stirred at this temperature for 1 hr. and poured into 1N sodium hydroxide solution (50 ml.). The mixture was extracted with methylene chloride, the extract washed with water and dried (Na_2SO_4). The methylene chloride solution was concentrated to ca.20 ml. by distillation and filtered through a column of neutral alumina (6 cm. x 2 cm. diam.) using ether (1 l.) as eluant. Evaporation of the ether and sublimation of the red waxy crystalline residue at 0.1 mm. (block temp. 80-5°), in darkness, afforded 3-formyl-6-methylpyrrolo[2,1-b]thiazole (0.686 g., 83%) as colourless feathery needles, m.p. 73-5° (softens and sublimes >70°), which rapidly become violet in the light.

Found: C,58.29; H,4.64; N,8.62.

C_8H_7NOS requires C,58.18; H,4.24; N,8.48%.

Reaction of 6-methylpyrrolo[2,1-b]thiazolium perchlorate with ethyl orthoformate.

1) To a solution of 6-methylpyrrolo[2,1-b]thiazolium perchlorate (0.474 g., 2 mmole) in warm (50°) ethanol (7 ml.) was added ethylorthoformate (2.96 g., 20 mmole) and the mixture cooled instantly to room temperature. The initially colourless solution became red on addition of the ester

and deposited red needles (0.494 g.) on cooling. The product was filtered off and washed well with ether. It contained some ethoxymethylene compound (theoretical yield 0.586 g.) together with monomethine dyestuff (theoretical yield 0.384 g.) affording an orange colour on treatment with 2,3-dimethylthiazolium perchlorate and an excess of pipiridine in ethanol.

2) To a solution of 6-methylpyrrolo[2,1-b]thiazolium perchlorate (0.474 g., 2 mmole) in cold acetonitrile (5 ml.) was added ethyl orthoformate (2. 96 g. 20 mmole) and the mixture allowed to stand at room temperature for 3 min. during which time the solution became yellow then pale red. Ether (20 ml.) was added precipitating a yellow floculent material (0.505 g.) which was filtered off, and washed well with ether. The product rapidly became red in air and could not be recrystallised as solutions of it rapidly became red on standing or warming.

The product (0.293 g., 1 mmole if pure ethoxymethylene compound) was added to a solution of 2,3-dimethylbenzothiazolium perchlorate (0.263 g., 1 mmole) in methanol (6 ml.) followed by piperidine (0.17 g., 2 mmole) and the mixture refluxed for 5 min. After cooling the precipitated 3-methyl-2-[2-(6-methylpyrrolo[2,1-b]thiazolyl) vinyl] benzothiazolium perchlorate (0.27 g., 65%) was filtered off, washed well with ether and recrystallised from acetonitrile as red-brown prisms with a green metallic lustre, m.p. 288-92°.

Found: N,7.17.

$C_{17}H_{15}ClN_2O_4S_2$ requires N,6.81%.

3) A solution of 6-methylpyrrolo [2,1-b] thiazolium perchlorate (0.474 g., 2 mmole) and ethyl orthoformate (0.888 g., 6 mmole) in ethanol (7 ml.) was refluxed for 5 min. The mixture was cooled and the material which crystallised (0.405 g.) was filtered off and washed well with ether. The product could not be recrystallised satisfactorily owing to the presence of what appeared to be polymeric material.

e) Nitrosation of 6-methylpyrrolo[2,1-b]thiazole.

A solution of sodium nitrite (0.105 g., 1.5 mmole) in water (1 ml.) was added with shaking to a solution of 6-methylpyrrolo 2,1-b thiazole (0.137 g., 1 mmole) in a mixture of concentrated hydrochloric acid (1 ml.) and water (4 ml.) at 0°. The yellow solution was allowed to stand at 0° for 15 min., diluted with water (100 ml.), potassium carbonate (10 g.) added and the mixture extracted with methylene chloride. The extract was dried (Na_2SO_4), the solvent evaporated and the residue crystallised from cyclohexane to afford mononitroso-6-methylpyrrolo[2,1-b]thiazole (0.162 g., 97%) as emerald green fibrous plates, m.p. 128.5-30° (decomposes to a black liquid).

Found: C,50.74; H,4.17; N,16.49.

$C_7H_6N_2OS$ requires C,50.59; H,3.64; N,16.86%.

Attempted oxidation of mononitroso-6-methylpyrrolo[2,1-b] thiazole to the mononitro compound.

1) To a solution of mononitroso-6-methylpyrrolo [2,1-b] thiazole (0.083 g., 0.5 mmole) in glacial acetic acid (5 ml.) was added 30% hydrogen peroxide (0.28 ml., 2.5 mmole) and the mixture heated at 100° for 1 hr. The

mixture was diluted with water (100 ml.), made alkaline with potassium carbonate and extracted with methylene chloride. The methylene chloride solution was dried (Na_2SO_4), the solvent evaporated and the residue (0.013 g.) examined by thin layer chromatography which showed the presence of unchanged starting material, a more polar yellow compound and even more polar material in a streak from the origin.

2) The above reaction was repeated using water (5 ml.) as solvent in place of glacial acetic acid. The product (0.03 g.) was similar to that obtained above but appeared to contain a slightly greater proportion of the yellow compound.

f) Trifluoroacetylation of 6-methylpyrrolo [2,1-b] thiazole.

To a solution of 6-methylpyrrolo [2,1-b] thiazole (0.685 g., 5 mmole) in dry methylene chloride (35 ml.) at room temperature was added a solution of trifluoroacetic anhydride (1.103 g., 5.25 mmole) in dry methylene chloride (35 ml.) dropwise, with stirring, over 20 min. After the completion of the addition the mixture was stirred for 4 hr. at room temperature, poured into a 1% aqueous solution of potassium carbonate (500 ml.). The methylene chloride layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent and distillation of the residual pale green oil at 0.1 mm. (block temp. 70-5°) afforded monotrifluoroacetyl-6-methylpyrrolo [2,1-b] thiazole (1.22 g. 98%) as pale yellow prisms which rapidly became green in air, m.p. 45-54°. The melting point was unaffected by further sublimations and the compound afforded only one spot on thin layer chromatography.

Found: N,6.25.

$C_9H_6F_3NOS$ requires N,6.01%.

Hydrolysis of monotrifluoroacetyl-6-methylpyrrolo[2,1-b]thiazole.

Monotrifluoroacetyl-6-methylpyrrolo[2,1-b]thiazole (0.233 g., 1 mmole) was refluxed with a solution of sodium hydroxide (0.1 g., 2.5 mmole) in a mixture of water (0.5 ml.) and methanol (1.5 ml.) for 2 hr. The mixture was cooled, diluted with water (200 ml.) and extracted with ether. The ether solution was washed with water, dried (Na_2SO_4) and the solvent evaporated affording unchanged trifluoroacetyl compound (0.055 g., 23 %). The combined aqueous solution and washings were made just acid with 0.5N sulphuric acid and the mixture extracted with ether. The ether solution was washed with water, dried ($MgSO_4$) and the solvent evaporated. The residue was taken up in the minimum volume of boiling cyclohexane-acetone (4:1), filtered, and the bulk of the acetone evaporated. On cooling 6-methylpyrrolo[2,1-b]thiazole monocarboxylic acid (0.125 g., 68%) crystallised as colourless plates with a grey metallic lustre, m.p.133.5-4° (with gas evolution).

Found: N,7.12.

$C_8H_7NO_2S$ requires N,7.69%.

g) Tropylation of 6-methylpyrrolo[2,1-b]thiazole.

1) Tropylium perchlorate (0.19 g., 1 mmole) was added to a solution of 6-methylpyrrolo[2,1-b]thiazole (0.137 g., 1 mmole) in acetonitrile (15 ml.). After standing at room temperature for 2 hr. the solution was poured into water (200 ml.) and the mixture extracted with ether. The ether solution was washed with water, dried (K_2CO_3)

and the solvent evaporated affording a yellow oil (0.211 g.). Examination of the product by thin layer chromatography showed that it consisted of two components one of which was present only to a small extent (~2%). The product did not form a crystalline complex with trinitrobenzene or trinitrofluorenone and decomposed extremely rapidly to a green-blue tar.

2) The above reaction was repeated using twice the stated quantity of tropylium perchlorate. The product, a viscous yellow syrup (0.343 g.) gave one spot on thin layer chromatography identical to the minor component of the product from the above reaction. The product could not be crystallised from a variety of solvents, did not afford a crystalline complex with trinitrobenzene or trinitrofluorenone and slowly darkened in air.

CV Reactions of methyl groups in pyrrolo[2,1-b]thiazoles.

a) Reaction of 3-methyl-6-phenylpyrrolo[2,1-b]thiazole with nbutyl lithium.

To a stirred solution of n butyl lithium (0.025 mole) in ether (20 ml.) at -15° under nitrogen was added a solution of 3-methyl-6-phenylpyrrolo[2,1-b]thiazole (4.26 g., 0.02 mole) in ether (30 ml.) and the mixture allowed to warm to room temperature. After stirring for 18 hr. atroom temperature the colourless mixture was treated with a solution of benzophenone (5.4 g., 0.03 mole) in ether (30 ml.). The mixture was poured into 5% ammonia solution (400 ml.) and the mixture extracted with ether. The ether solution was washed with water until free of ammonia and dried ($MgSO_4$). Evaporation of the solvent afforded a brown viscous oil (9.4g.) which was analysed by thin layer chromatography. This showed the presence of only unchanged 3-methyl-6-phenylpyrrolo[2,1-b]thiazole and benzophenone.

b) Reaction of 1,2,3-trimethylpyrrolo[2,1-b]thiazole with tetrachloro-1,2-benzoquinone.

A solution of tetrachloro-1,2-benzoquinone (0.738 g., 3 mmole) in acetonitrile (12 ml.) was added to a solution of 1,2,3-trimethylpyrrolo[2,1-b]thiazole (0.495 g., 3 mmole) in acetonitrile (8 ml.) at room temperature. The colour of the quinone was discharged instantly with the depcsition of a white solid. After standing for 4 hr. at room temperature the colourless granules of 5,7-bis-(2,3,4,5-tetrachloro-6-hydroxyphenoxymethyl)-6-methyl-pyrrolo[2,1-b]thiazole (1.025 g., 83%) were filtered off,

washed with acetonitrile (10 ml.) and dried in vacuo, m.p. 150-166° (decomposes to a black liquid, darkens >120°). The material could not be recrystallised as it gave violet solution on heating in a variety of solvents.

Found: C,38.63; H,1.82.

$C_{21}H_{11}Cl_8NO_4S$ requires C,38.35; H,1.68%.

Cleavage of 5,7-bis-(2,3,4,5-tetrachloro-6-hydroxyphenoxymethyl)-6-methylpyrrolo[2,1-b]thiazole with acid.

A solution of 5,7-bis-(2,3,4,5-tetrachloro-6-hydroxyphenoxymethyl)-6-methylpyrrolo[2,1-b]thiazole (0.657 g., 1 mmole) in glacial acetic acid (10 ml.) containing perchloric acid (1 ml.) was allowed to stand at room temperature for 24 hr. The solution was poured into water (200 ml.) and the mixture extracted with ether. The ether solution was extracted with N sodium hydroxide solution (3 x 25 ml.). The combined alkaline extracts were acidified with sulphuric acid and the product extracted with ether. The ether solution was washed with water, dried ($MgSO_4$) and the solvent evaporated. Crystallisation of the colourless residue from glacial acetic acid afforded tetrachlorocatechol, (0.21 g., 43%) as colourless needles, m.p. and mixed m.p. 193-4°.

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